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Improving adherence to blood pressure lowering medication

Improving adherence to blood pressure lowering medication

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Abstract

Lack of adherence to long-term therapies has been recognised for many years as a major problem, commonly undermining the effectiveness of medical care. The main objectives of this thesis were to evaluate the effect of nurse-led adherence support compared with usual care on adherence, blood pressure and costs, and to compare a newly developed adherence self-report tool with electronic monitoring.

A total of 245 uncontrolled hypertensive patients with a diagnosis of essential hypertension were recruited in 22 general practices in Avon.

A validation study of an adherence self-report tool compared with electronic monitoring showed that self-report can predict timing compliance at higher levels of adherence. More research is needed on the usefulness of this tool in day-to-day practice and in a more representative study sample.

The main study of this thesis, the RCT, compared a nurse-led adherence support consultation followed by a re-inforcement appointment two months later with usual care alone. The main outcomes in this RCT were adherence to blood pressure lowering medication ('timing compliance'), systolic and diastolic blood pressure, and costs.

There was no evidence of an effect of nurse-led adherence support on timing compliance (difference between means: -1.0, 95% CI: -5.1 to 3.1, p=0.63), systolic blood pressure (difference between means: -2.7 mmHg, 95% CI: -7.2 to 1.8, p=0.24) or diastolic blood pressure (0.2, 95% CI: -1.9 to 2.3, p=0.85). With respect to the evaluation of the adherence self-report tool, there is strong evidence that a reduction of one level of self-reported adherence is associated with a decrease in timing compliance of around 5% (p=0.0004).

In conclusion, nurse-led adherence support was no more effective than usual care in terms of increasing adherence or reducing blood pressure. Baseline adherence levels were high in both comparison groups, leaving little room for further improvement. In the few participants who did have medication problems, the intervention appeared to be successful, but further research is needed to consolidate this finding.

Acknowledgements and dedication

I owe my greatest debts to my supervisors and mentors, Tom Fahey and Tim Peters, who with their inspiration and enthusiasm for primary care research have greatly influenced me. Without their generous support, kind encouragement and gentle advice this thesis would never have been written.

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I dedicate this thesis to my wife Sharmila, who showed endless patience and understanding, and our two sons, Kiran and Rohan.

Author's declaration

I declare that the work in this dissertation was carried out in accordance with the Regulations of the University of Bristol. The work is original except where indicated by special reference in the text, and no part of the dissertation has been submitted for any other degree.

I was principal investigator in this study and took the lead role in study design, data collection, data analysis and writing. My supervisors, Tom Fahey and Tim Peters, were co-applicants for the research grant and had the original idea for the research. Both were closely involved in the study and assisted with practical issues, clinical matters and statistical methods. Shah Ebrahim was co-author on the Cochrane systematic review.

Any views expressed in the dissertation are those of the author and in no way represent those of the University of Bristol.

The dissertation has not been presented to any other University for examination either in the United Kingdom or Overseas.

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Publications, presentations and further funding relating to this thesis

Publications arising from this thesis

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Schroeder K, Ebrahim S, Fahey T, Montgomery A, Peters T. Conflicting evidence for effect of dosing schedules on compliance (letter). *British Medical Journal* 2002;**324**:425.

Schroeder K, Montgomery A, Ebrahim S. Pharmacological properties of antihypertensive drugs need to be acknowledged (letter). *British Medical Journal* 2001;**323**:1129-30.

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Fahey T, **Schroeder K**. High blood pressure. In: Oxford Textbook of Primary Medical Care, Volume 2, Section 1. Editors: Jones R, Hobbs R. *Oxford University Press* 2003, in press.

Presentations

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1 Introduction

In this first chapter I introduce the problem addressed in this thesis and give a brief outline of the current knowledge in the field of medication adherence. I also summarise the aims of this research and provide a general overview of the thesis with an outline of the remaining chapters.

1.1 Background and context for the thesis

1.1.1 The problem of non-adherence

The term 'non-adherence' is commonly used in the literature but not entirely helpful, because it assumes that people can either be 'adherent' or 'non-adherent'. However, adherence to medication should be treated as a continuous variable as described later in this thesis, and the term 'non-adherence' relates in fact to sub-optimal or poor adherence. Poor adherence to long-term therapies in chronic disease is common and can severely undermine the effectiveness of medical care.[1] The World Health Organization (WHO) has recognised this as an international problem and recently published a report *Adherence to Long-term Therapies: Policy for Action* to address this topic.[2] The aim of this WHO report is to identify global issues around medication adherence in important medical conditions and to provide guidance on improving the cost-effectiveness of health care interventions. This report illustrates that adherence is influenced by various factors, which include social and economic circumstances, the health care team and system, manifestations of the disease, characteristics of the therapy, and patient-related factors.

Unfortunately, a number of terms are – often interchangeably – being used to discuss medication adherence, including compliance, concordance, or persistence, which can be rather unhelpful. In this thesis I will mainly use the term adherence for reasons outlined in the next chapter, where I will define and contrast these terms in more detail.

For many decisions made in primary care, both in the field of adherence and in many other areas, there appears to be a lack of a sound evidence base.[3] Surprisingly, there has been little improvement of understanding in the field of adherence.[4] This is partly due to the fact that medication adherence in chronic disease is an immensely complex topic and has led to a proliferation of studies, editorials and research letters in this field, which are of varying and often poor quality.

Many issues around the research methodology remain unclear and continue to pose challenges to researchers and clinicians alike, including the definition and measurement of adherence. Although many advances have been made in recent years, particularly in the measurement of adherence with the advance of electronic monitoring, a number of questions still remain unanswered largely unanswered: How should we define adherence? How should we measure adherence? What is the true level of adherence in the community? What interventions work to improve adherence? How does adherence relate to clinical outcomes? What do patients think about adherence?

1.1.2 Non-adherence in hypertension

This thesis will examine ways to improve adherence in chronic disease, using hypertension as a specific example. It is widely acknowledged that hypertension is a major risk factor for cardiovascular disease. There is strong evidence from high quality randomised controlled trials (RCTs) that treating high blood pressure with medication can substantially reduce the risk of heart attack and stroke. The results of major systematic reviews suggest that reducing diastolic blood pressure by 5 to 6 mmHg reduces the risk of coronary heart disease by 20 to 25% and of stroke by 35 to 40%, which is of substantial public health importance.[5,6]

However, the control of high blood pressure in the community is far from optimal, with lack of medication adherence (estimated to be only around 50 to 70% in uncontrolled hypertensive people[7,8]) likely to be a major factor.[9-11]

1.2 The need for research

So if lack of adherence to medication contributes to such an extent to poor control of high blood pressure in the community, how can we improve medication adherence effectively? A recent attempt at answering this question is not very encouraging, as the latest systematic review of RCTs of interventions to assist patients to follow prescriptions of medications concludes:

> *"Current methods of improving medication adherence for chronic health problems are mostly complex, labor-intensive, and not predictably effective. The full benefits of medications cannot be realised at currently achievable levels of adherence; therefore, more studies of innovative approaches to assist patients to follow prescriptions for medications are needed."*[12]

A Working Party on Concordance in the UK has also recently addressed the problem of non-adherence.[13] It recognises the need for a multi-disciplinary approach to research into medicine taking and the process of prescribing and also addresses the need for effective strategies to improve adherence to medication. The working party also introduced the new concept of 'concordance', which emphasises the importance of a partnership between prescribers and patients for an effective use of medication.

It has become evident that new approaches to increase adherence are urgently needed that are easy to implement, cost-effective, and acceptable to patients and health professionals alike.[4]

1.3 Aims of the research

This thesis aims to investigate new ways to improve adherence to medication in chronic disease, taking into account previous research and the above recommendations, and using hypertension as the target condition.

Adherence to medication is closely related to four interacting elements, which include (1) condition-related factors such as the severity of the disease, symptoms experienced by the patients or the rate of progress, (2) characteristics of therapies like side effect and complexity of the treatment regimen, (3) health care team and system-related factors such as the organisation and delivery of care, and (4) patient-related factors, which may include health beliefs and knowledge about high blood pressure.[2,4] The research described in this thesis focuses on how addressing health care team and patient related factors may help to improve adherence to blood pressure lowering medication. It also tries to acknowledge and address the fact that it is the patient's agenda that determines whether patients choose to take their medicines or not.

The objectives of the studies covered by this thesis are to:

1. Conduct a systematic review of randomised controlled trials evaluating the effectiveness of interventions to increase adherence to blood pressure lowering medication
2. Evaluate a nurse-led intervention to increase adherence to blood pressure lowering medication in a RCT
3. Compare a newly designed adherence self-assessment tool with electronic monitoring

4. Obtain new data on medication taking in people with high blood pressure by using electronic medication monitors to measure adherence
5. Add to the evidence base on improving the management of chronic conditions in primary care, using hypertension as an example

The overall concern of this thesis is to provide answers to research questions that may have a positive impact on patients and health professionals lives in day-to-day primary care.

1.4 Outline of the remaining chapters

Chapter 2 reviews the literature in the field of adherence in hypertension and provides a general and broad overview of important adherence related topics.

Chapter 3 is a systematic review of interventions to increase adherence to blood pressure lowering medication. This systematic review complements the above broad literature review, but is different in its methodology and designed to provide a basis for the trial as the main study of this thesis by reviewing RCTs of interventions to improve adherence to blood pressure lowering medication in more detail.

Chapter 4 gives a general overview of methodological issues around adherence research, discussing the implications of the literature review for the design of the studies, the choice of methods and ethical implications.

Chapter 5 outlines the methods used for the RCT, which is the main study of this thesis, including details about the conduct and analysis of the study.

Chapter 6 presents a study that evaluates an adherence self-report questionnaire to identify non-adherence, which uses electronic monitoring as the comparison.

Chapter 7 presents the RCT results, with an emphasis on describing the effect of the intervention on adherence and blood pressure.

Chapter 8 contains a description of an economic evaluation within the RCT, focusing on costs at the general practice level.

Chapter 9 discusses the findings of this thesis in the light of previous research, taking into account methodological limitations that may have affected the results.

The final Chapter 10 concludes with recommendations for clinical practice and future research.

2 Overview of the literature

2.1 Introduction

The first chapter summarised briefly why improving medication adherence in hypertension is important. To put the studies described in this thesis into context, the next two chapters aim to provide a broad and comprehensive overview of the theories behind research on medication adherence, with an emphasis on the field of hypertension. I outline current controversies, summarise recent developments and identify future research trends in adherence related research. Both chapters critically evaluate work that has been conducted by other researchers in this area to provide a theoretical basis for the research described in this thesis and to indicate how this thesis might add to the current body of knowledge.

2.1.1 Issues around the literature search

Promoting adherence to medical treatments has long been a central aspect of medical care and is almost as old as medicine itself. Hippocrates wrote:

> *"The physician must not only be prepared to do what is right himself, but also to make the patient...cooperate"(Hippocrates, 5th century B.C.)*[14]

Although this paternalistic view of the relationship between patients and health care providers has become outdated in modern times, promoting patient adherence to treatment is still an important aspect of patient care. More and more powerful and effective treatments have become available in recent years for many chronic conditions. These therapies can only provide benefit if adherence to treatment is present to a certain level.

Although the evaluation and subsequent improvement of adherence to medical treatments have been the focus of research for many years, studying this field is still a less than perfect science for a number of reasons. Most importantly, measuring adherence is far from straightforward. Using hypertension as an example, a variety of different methods to measure adherence have been used, all of which are imperfect at best.[15] To make matters even more complicated, all measures of adherence obtained through the various methods can be expressed in different ways, making comparison of study results particularly difficult (see 2.4.4 Measuring Adherence). The level of

adherence to treatment regimens also depends on a variety of different factors, which may for instance be related to the therapy itself, the health care setting or any views that patients may have about the treatment.

Reviewing the literature in this field is therefore challenging. It is also based on judgements about the relative importance of individually published research. This broad and, where appropriate, detailed review therefore uses a perspective that focuses on the pragmatic implementation of adherence improving strategies in primary care, which is the main topic of this thesis.

2.2 General review methodology

2.2.1 Review structure

The following sections in this review aim to cover the main concepts, theories and methodological approaches, including the assumptions and definitions other researchers have employed, and the subheadings are as follows:

A review of hypertension in primary care (Section 2.3)

This provides a brief review of the diagnosis and management of hypertension in primary care with an emphasis on topics relating to medication adherence. This will also include an evaluation of the literature on new developments in hypertension management in the UK.

A review of general concept in adherence research (Section 2.4)

This section critically evaluates the problems of medication adherence in a broader sense, as described in the research literature. It includes a summary and discussion of the terminology and the methods used in adherence research. It also outlines important psychological models and cognitive aspects of adherence in so far as they are important for an understanding of adherence related behaviour and the development of the intervention tested in the RCT.

Adherence in hypertension (Section 2.5)

This section focuses on the particular issues around adherence in the field of hypertension. It includes research on the specific differences of adherence in

hypertension compared to other conditions. It also covers concepts such as side effects, motivation, health beliefs, and knowledge about hypertension, in so far as they are important with respect to blood pressure lowering medication.

2.2.2 Search strategy

The literature search aimed to identify all the relevant material that was needed to inform and further clarify the research question. The following electronic databases provided the starting point for the search: *The Cochrane Controlled Trials Register*, MEDLINE, EMBASE, the *Cumulative Index of Nursing and Allied Literature* (CINAHL), and the *National Research Register* (NRR) were searched to identify ongoing studies and unpublished research.

The initial search used the following search terms alone and in combination, with slightly amended search strategies for the individual databases and for the particular topics that were being searched: "adher*", "compli*", "concord*", "hypertens*", "blood pressure*". This search revealed more than 1000 titles and abstracts of articles. I identified potentially relevant articles by reading the titles and abstracts and retrieved all 133 publications that appeared relevant.

I identified further literature through personal communications with colleagues and study authors, screening the reference lists of all retrieved articles, reviewing abstracts of scientific meetings and by contacting experts in the field. The search was not limited to English literature and, where possible, I obtained help with translating articles published in other languages. Unpublished studies, theses, dissertations and studies published in non-peer reviewed journals were considered for inclusion in the review if these seemed relevant and of sufficient scientific rigour. I identified newly published papers at any time during the study period by screening the lists of contents of relevant journals and included these in the review where appropriate.

2.2.3 Important topics covered in the review

There are a number of issues that need to be considered when investigating adherence. This includes a definition of terms, which is particularly confusing in the field of medication adherence and has led to a continuing debate. Measuring adherence is likewise difficult and challenging. This chapter will therefore also look at various ways to measure adherence, and how the review of these methods led to the choice of measurement instruments used in this study. Hypertension is a chronic condition that

often does not cause any symptoms. Its treatment is frequently associated with unwanted effects of blood pressure lowering medication, which may be one of the factors affecting patient adherence to treatment. Last but not least, the literature review covers the involvement of patients in their care, which is of paramount importance when trying to increase adherence.

2.3 A review of hypertension in primary care

The following section gives an overview of issues around the management of hypertension in primary care. There is a focus on areas that either help understand problems around medication adherence, or that have provided a basis for the methods used in the studies described later.

2.3.1 Definition of hypertension

So far there is no generally accepted definition of high blood pressure, and despite good evidence from high quality randomised controlled trials, current guidelines are different in their emphasis and content.[16] Fahey & Peters found in a cross-sectional study in 18 general practices in Oxfordshire that the proportion of patients with controlled hypertension varied from 17.5% to 84.6% between different international guidelines. They concluded that the present guidelines are inconsistent in their recommendations with regard to what constitutes controlled blood pressure and that clarification about absolute benefits and risks of treatment is warranted.[17]

National guidelines from the US define resistant hypertension as blood pressure that cannot be reduced to values below 140/90 mmHg in people who take adequate triple drug regimens in the correct dosage.[18] Although this definition covers many people with high blood pressure, it does not include those for whom the target blood pressure should be even lower. In the UK, the treatment thresholds in people with sustained high blood pressure used to be equal to or more than 160 mmHg for systolic and equal to or more than 100 mmHg diastolic, with different thresholds and targets for people with diabetes or evidence of target organ damage, cardiovascular disease, or a 10-year coronary heart disease risk of equal to or more than 10% according to the Joint British Societies Coronary Heart Disease risk assessment programme and risk chart.[19] However, the suggested thresholds have recently been lowered to 140 mmHg and/or 90 mmHg, which increases the 'pool' of those individuals who potentially need to be treated.[20]

2.3.2 Epidemiology

Blood pressure is a normally distributed characteristic in a population.[21] The estimated prevalence of hypertension depends on the blood pressure level used to define the condition, which is arbitrary.[22,23] Even when using higher cut-off points for the diagnosis of hypertension, though, high blood pressure is common. Overall, 15% of the UK population take antihypertensive drugs to lower their blood pressure. The prevalence increases sharply in the elderly, to up to 30%. Subsequently, treatment for high blood pressure is one of the commonest reasons to visit a family physician. In the UK, 16% of people aged 65 to 74 and 14% of people aged between 75 and 84 visit their general practitioner with high blood pressure.[21]

There is some evidence to suggest that detection, treatment and control of high blood pressure has improved over the past 25 years in the United States.[18] However, Colhoun and colleagues have shown in a survey of 12116 adults in England who participated in the 1994 Health Survey for England that the control of blood pressure has remained inadequate. [9] Even when a liberal criterion of 160/95 mmHg was used, only 30% were adequately controlled, although 50% of individuals with high blood pressure were taking antihypertensive drugs. Thus there appears to be considerable scope for improving the management and subsequent control of high blood pressure in England.

2.3.3 Diagnosis

High blood pressure is an asymptomatic condition and is usually detected through case finding by health professionals. Very rarely, patients may present to their GP with symptoms of malignant hypertension. In such patients, the commonest symptoms are headache, visual disturbance, dyspnoea due to heart failure, and gastrointestinal symptoms such as anorexia, nausea, and vomiting.[23]

Assessment

When assessing a patient with suspected high blood pressure, the objective is to simultaneously evaluate cardiovascular risk, end-organ damage, and likely contributory factors.[19] The initial approach should start with a careful history with a focus on other symptoms, cardiovascular risk factors, and other medications. Physical examination usually includes assessment of height and weight (to calculate the body mass index, BMI), and looking for end-organ damage, such as fundal haemorrhages or evidence of

heart failure. Basic investigations aim to provide further information on additional risk factors (urinalysis for glycosuria, total:HDL cholesterol) or end-organ damage (urea, electrolyte and creatinine levels, urinalysis for proteinuria). The accuracy and reliability of many of the elements of the history, examination, and investigations undertaken when assessing patients with high blood pressure is however unknown.[22]

Blood pressure measurement

Careful attention to blood pressure measurement technique is necessary, so that the accuracy and reliability of this diagnostic test is maximised.[19,22,24] Accurate measurement of blood pressure is important for clinical management and in the conduct of research, and taking a patient's blood pressure should follow current consensus guidelines (Figure 1).[19,21]

Figure 1 Consensus guidelines for the measurement of high blood pressure[21]

- The patient is sitting in a quiet environment with the right arm resting on a support that places the midpoint of the upper arm at the level of the heart
- Measure sitting blood pressure routinely; standing blood pressure in elderly and diabetic patients
- Use cuff of appropriate size (bladder should encircle equal to or more than 80% or the arm, and the lower edge should be two cm above the antecubital fossa)
- Inflate cuff rapidly to 70 mmHg and then inflate by 10 mmHg increments palpating the radial pulse until the pulse disappears. Note the pressure at which the pulse disappears and subsequently reappears during deflation
- Place the low-frequency bell over the brachial artery pulsation
- Inflate the bladder 20 mmHg above the level previously determined by palpation. Deflate bladder by 2 mmHg per second. Note the systolic blood pressure level with the appearance of repetitive sounds (Korotkoff phase 1) and measure diastolic blood pressure at the disappearance of sounds (Korotkoff phase 5). Systolic and diastolic blood pressures should be rounded to the nearest 2 mmHg.
- Take two measurements at each visit, at least more than 30 seconds apart
- Use the average for several visits (≥ three) when estimating sustained blood pressure readings.

Source: Ramsey et al. Guidelines for the management of hypertension: report of the third working party of the British Hypertension Society. J Hum Hypert 1999;13:569-92.

Health professionals should be aware of patient, health professional and instrument factors that may lead to inaccurate blood pressure measurement.[22,24] The commonest reasons include the use of an inappropriately small cuff, deflating the cuff too quickly, failing to palpate the maximal systolic blood pressure before auscultation, and 'rounding' errors when recording blood pressure readings.

Mercury sphygmomanometers are likely to be phased out for health and safety reasons. There will be increasing use of alternative devices to measure blood pressure including aneroid, semi-automated, and automated devices. Substantial evidence has emerged that these alternative devices can be inaccurate when subjected to validation. Regular calibration is also required, particularly of aneroid sphygmomanometers.[19]

2.3.4 Management in primary care

On a national level, the management of high blood pressure is addressed through the National Service Frameworks (NSFs) for Coronary Heart Disease and for Older People, which support the implementation of management strategies for hypertension particularly in primary care.[25,26] These documents mainly advocate improved protocols to assess, treat and follow-up people with established coronary heart disease and emphasise the importance of appropriate lifestyle changes and the correct use of medication to treat high blood pressure.

The principal objectives when managing high blood pressure are to:[22]

1. Decrease cardiovascular risk associated with hypertension
2. Decrease the risk of any other co-existing cardiovascular risk factors
3. Select antihypertensive drugs that are likely to do more good than harm for each individual's mix of co-existing medical conditions, risk factors, preferences, and social circumstances
4. Minimise the adverse effects and inconvenience of antihypertensive drugs.

Non-pharmacological treatment

Risk factor modification is frequently recommended as an initial alternative to drug treatment.[27]

The latest systematic review of long-term effects of advice to reduce dietary salt in adults by Hooper and colleagues evaluated three trials in normotensive people

(n=2326), five trials in those with untreated hypertension (n=387), and three trials in people being treated for hypertension (n=801) with follow-up from six months to seven years.[28] Intensive behavioural interventions, which are likely to be unsuitable to primary care or population prevention programmes, reduced systolic blood pressure by 1.1 mmHg (95% confidence interval (CI): 1.8 to 0.4 mmHg) and diastolic by 0.6 mmHg (95% CI: 1.5 to -0.3 mmHg). This review concluded that advice to reduce sodium intake may help people on blood pressure lowering drugs to stop their medication while maintaining good blood pressure control.

In a recent RCT, Blumenthal and colleagues randomly assigned 133 sedentary, overweight men and women with unmedicated high normal blood pressure or mild hypertension to aerobic exercise alone or in combination with a behavioural weight management programme. Weight management was associated with a 7 mmHg systolic and a 5 mmHg diastolic net reduction in clinic blood pressure, compared with a 4 mmHg systolic and diastolic blood pressure reduction associated with aerobic exercise ($p<0.001$, 95 % confidence interval (CI) not reported).[29]

Whelton and colleagues performed a meta-analysis of 54 RCTs with a total of 2419 participants investigating the effect of aerobic exercise on blood pressure.[30] Aerobic exercise was associated with a significant reduction in mean systolic (-3.84 mmHg, 95% CI: -4.97 to -2.72 mmHg) and diastolic blood pressure (-2.58 mmHg, 95% CI: -3.35 to -1.81 mmHg).

In summary, there appears to be an effect of lifestyle interventions on blood pressure, but the magnitude of blood pressure reduction for most interventions is fairly modest.[21,31]

Pharmacological treatment

A wide choice of antihypertensive agents is available for the treatment of high blood pressure in general practice, which usually allows practitioners to select an appropriate drug or drug combination for individual patients. The six main therapeutic drug classes include diuretics, beta blockers, calcium channel blockers, ACE inhibitors, angiotensin II antagonists, and alpha-1-adrenoceptor blockers.[19]

Collins & Peto summarised the effects of antihypertensive drug therapy on stroke and coronary heart disease and reviewed four large and 13 small unconfounded randomised controlled trials, reported between 1965 and 1992.[5] Their results indicated strong

evidence that reducing diastolic blood pressure by 5 to 6 mmHg leads to a reduction in stroke of 38% (95% CI: 31 to 45%) and in coronary heart disease of 16% (95% CI: 8 to 23%). There has been a move away from the 'stepped care' approach of drug treatment which included starting with a thiazide diuretic or beta blocker and than adding in other classes of antihypertensive drugs. A 'tailored care' approach is now favoured, which individualises drug therapy to the patient's risk factor and comorbidity profile (see Table 1).

Table 1 Indications, contra-indications and adverse effects of major antihypertensive drug classes

Drug class	Indications	Contra-indications	Common adverse effects
Thiazide diuretics	Elderly Diabetes (type 2) African-Carribean ethnic groups	Gout Dyslipidaemia Urinary incontinence	Hypokalaemia Hyponatraemia Sexual dysfunction Gout Glucose intolerance
Beta-blockers	Myocardial infarction Angina Heart failure Migraine	Asthma/COPD Heart block PVD Dyslipidaemia	Fatigue Insomnia Cold peripheries Bradycardia
ACE inhibitors	Diabetes Myocardial infarction Angina Heart failure Chronic renal disease	Pregnancy Renovascular disease PVD	Cough First dose hypotension Taste disturbance Angio-oedema
Calcium-channel blockers	Elderly Angina Pregnancy African-Carribean ethnic groups	Myocardial infarction Heart failure	Constipation Peripheral oedema Flushing Headache
Alpha blockers	Prostatism	Heart failure Urinary incontinence Postural hypotension	Nasal stuffiness Dizziness Postural hypotension

Source: Fahey & Schroeder. High blood pressure. In: Oxford Textbook of Primary Medical Care, 2003[21]
ACE = angiotensin converting enzyme; COPD = chronic obstructive pulmonary disease; PVD = peripheral vascular disease

Thiazide diuretics are still the preferred initial therapy for hypertension. One of the most important trials of antihypertensive therapy, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which studied 33357 participants with hypertension in 623 North American centres, aimed to determine whether treatment with a calcium channel blocker or an angiotensin converting enzyme inhibitor lowers the incidence of coronary heart disease or other cardiovascular disease events versus treatment with a diuretic.[32] The primary outcome was combined fatal or non-fatal myocardial infarction, analysed by intention-to-treat. After a mean follow-up of 4.9 years there was no difference between the effects of chlorthalidone, amlodipine and lisinopril (relative risk (RR) 0.98 (95% CI: 0.90 to 1.07) for amlodipine and RR 0.99 (95% CI: 0.91 to 1.08) for lisinopril. The results of this study are consistent with findings from the HANE study, which compared hydrochlorothiazide with atenolol, nitrendipine, and enalapril.[33]

Despite these findings, Bloom argued in a recent editorial in the British Medical Journal that newer drugs in hypertension should help improve compliance.[34] Although this notion would be a convenient marketing strategy for the pharmaceutical industry, this is certainly untrue in the field of hypertension. There is good evidence that for the treatment of high blood pressure, low dose diuretics are as effective as more expensive antihypertensive drugs and often have also a better side effect profile than many newer drugs.[35,36]

Recent guidelines on the combination of drugs in the treatment of hypertension suggest to use angiotensin receptor blockers (A) or beta blockers (B) for renin-dependent hypertension and to prescribe calcium channel blockers (C) or diuretics (D) in the majority of hypertensive patients who have low-renin hypertension, which led to development of the AB/CD rule.[36]

A recent meta-analysis by Staessen and colleagues indicated that most antihypertensive drugs have similar long-term efficacy and safety and that their main effect is mediated through blood pressure control rather than individual pharmacological properties.[37] Combination drug therapy will frequently be necessary to achieve and maintain lower blood pressure goals.[38] Treatment of older people with hypertension is also effective. Mulrow and colleagues conducted a systematic review of 15 randomised trials, which involved a total of 21908 elderly persons, and found that treating older persons with hypertension is effective, with event rates for cardiovascular morbidity and mortality reduced from 177 to 126 events (95% CI: 31 to 76).[39] There is increasing evidence that

antihypertensive treatment may also protect against dementia in older people with systolic hypertension in addition to reducing the risk of heart attack and stroke.[40]

Long-term care

The main aims for the long-term care of people with high blood pressure are to ensure that blood pressure is at target level and to treat relevant co-morbid conditions.[21] Intensive lowering of blood pressure has been shown to reduce cardiovascular disease.[37] Randomised trials that compare aggressive versus less aggressive lowering of blood pressure report no adverse J-shaped relationship (too great a lowering of blood pressure leading to an increase in cardiovascular events).[41] The optimal target blood pressure has been proposed as less than 140/90 mmHg for non-diabetic patients and less than 140/80 mmHg for diabetic patients.[19]

The problem of uncontrolled hypertension

The care that patients with high blood pressure receive is often variable and incomplete. The consequence is that in many countries a large proportion (usually in the range of 40 to 50%, depending on the blood pressure level used to define target blood pressure) of patients taking antihypertensive drugs have not reached target blood pressure goals.[41] These individuals are said to have 'uncontrolled' high blood pressure, although it is worth emphasising again that every threshold for determining blood pressure control is arbitrary. However, there appears to be a linear and positive relationship between blood pressure and the risk of stroke, which suggests that lowering blood pressure leads to lower risk of disease.[5] There are a number of common reasons and proposed solutions if individuals do not reach target blood pressures (see Figure 2).[42]

We have recently conducted a systematic review of organisation and delivery of care interventions used to improve the control of blood pressure in patients with hypertension of 54 studies.[43] Although the methodological quality of studies was variable, there was good evidence from a single large RCT that regular review together with vigorous antihypertensive therapy reduces all-cause mortality.[44] Other interventions such as self-monitoring of blood pressure led to moderate reduction in blood pressure (weighted mean difference (WMD) -2.25 mmHg, 95% confidence interval (CI: -3.22 to -1.29), whereas educational interventions aimed at health professionals or patients did not appear to be associated with large net reductions in blood pressure.[43]

There is inadequate evidence to recommend an optimal timing for patient review, self-management strategies (including self-monitoring by patients), and the value of dedicated hypertension clinics. There is evidence that increased involvement of the primary health care team, particularly practice nurses, improves blood pressure control and prevents cardiovascular disease. The same can be said for structured care, which may include registration of patients, organised recall and regular review. However, the cost-effectiveness of such intensive approaches to long-term care is less certain.[43]

The British Hypertension Society Guidelines for the Management of Hypertension make important recommendations on how hospital and general practitioners should approach the management of hypertension.[19] However, the translation and adaptation of these recommendations into local guidelines and summaries will be an ongoing challenge and should be monitored through clinical audit. This has so far shown significant variability among practices and practitioners, which makes comparison between audits difficult.[45,46]

Figure 2 Causes of 'uncontrolled' hypertension and proposed solutions

Inaccurate blood pressure measurement	Follow BHS guidelines for the management of hypertension,[19] use standardised electronic blood pressure measurement devices
White-coat hypertension	Ask other health workers to measure patient's blood pressure; if still raised, try self-monitoring or referral for ABPM.
Disease progression	Can only be attributed to disease progression after excluding other possible causes.
Sub-optimal treatment	At least half the patients with high blood pressure will require two or more classes of antihypertensive drugs to ensure adequate blood pressure control.
Non-adherence to antihypertensive drugs	There is some evidence that adherence can be enhanced by educating and discussing adherence related issues with patients and by involving other members of the primary health care team.[41]
Concurrent use of antagonising drugs	Several drugs raise blood pressure and these should be specifically asked about when taking a history. Of particular note, NSAIDs are commonly prescribed, particularly in the elderly. It is estimated that these drugs increase blood pressure by about three to five mmHg in hypertensive individuals.
Co-existing conditions	Includes excessive alcohol use, obesity, anxiety, hyperinsulinism with insulin resistance, sleep apnoea, and smoking.
Secondary hypertension	Requires further investigation and specialist referral.

Adapted from: O'Rorke & Richardson. Evidence based management of hypertension: what to do if blood pressure is difficult to control. BMJ 2001;322:1229-32.
ABPM = ambulatory blood pressure monitoring
NSAID = non-steroidal anti-inflammatory drug

Non-adherence and non-response

In clinical practice a major problem is to differentiate between non-adherence to blood pressure lowering medication and non-response to treatment, which I will discuss in more detail in section 2.4.5.

2.3.5 Implications of diagnosing and managing high blood pressure

There is some evidence of a 'labelling' effect on patients diagnosed as having high blood pressure. Knowledge that a person has high blood pressure has been reported to increase their absenteeism from work and produce a negative impact on self-reported psychological well-being.[47] However, the overall impact of high blood pressure on quality of life is not thought to be substantial.[22]

Symptomatic adverse effects vary by drug class and by agents within drug classes. Overall, 10 to 18% of individuals receiving antihypertensive treatment report side effects (see also Table 1).[22] It is, therefore, important that general practitioners and other health care professionals involved in the care of people with high blood pressure are aware of the common adverse effects from the major classes of antihypertensive drugs.

2.3.6 Hypertension in the context of cardiovascular disease

It is important not to look at high blood pressure in isolation, but to see this as one of the risk factors for cardiovascular disease, which is the most important cause of death today.[48,49] The UK Department of Health aims to reduce cardiovascular disease in people under 75 years of age by two fifths before the year 2010,[25] which is expected to result from interventions in hypertension and other cardiovascular risk factors such as smoking, diabetes, and hypercholesterolaemia for primary prevention. Rather than using individual risk factors, risk assessment combining multiple risk factors is preferable but associated with practical problems.[50] Cardiovascular risk can be calculated using different risk calculation tools in general practice, which can be difficult if data on risk factors is not available.[51,52] In a study in which general practitioners and practice nurses compared the New Zealand risk tables with a reference calculation of risk, accuracy was only moderate.[53]

Dose-response relationships indicate that a given change in blood pressure leads to a reduction in cardiovascular risk by a constant proportion, irrespective of the starting level of blood pressure.[41,54] Interventions aiming to change risk factors should therefore be determined by an individual's level of risk and not necessarily based on the blood pressure level alone.[54] In addition, patient preferences always need to be taken into account when making evidence-based decisions in hypertension treatment. Practitioners should share decisions with patients, who are the experts in judging their own values and whose risk judgements may differ, either qualitatively or quantitatively.[55-58]

2.3.7 The role of nurses in the management of hypertension

Effectiveness of nurse-led care in general

General practitioners, nurses and other health professionals in the primary health care team work collaboratively to achieve the aim of improving and maintaining patients' health. However, the working relationship between nurses and doctors has not always been straightforward. Britain's National Health Service and primary care have undergone many organisational changes in recent years, and the role of nurses is expanding.[59,60]

A recent systematic review by Horrocks and colleagues of whether nurse practitioners working in primary care can provide equivalent care to doctors included 11 trials and 23 observational studies.[61] This review showed that patients were more satisfied with the care by a nurse practitioner (standardised mean difference 0.27, 95% CI: 0.07 to 0.47), although the effect size was relatively small. Nurse practitioners were found to have longer consultations and they requested more investigations. This study found no differences in prescriptions, return consultations, or referrals. The results of this review suggest that an increase in the availability of nurse practitioners may lead to higher levels of patient satisfaction and quality of care.

The British Medical Journal devoted a special theme issue focusing on this area in April 2000, looking at new ways of how nurses and doctors can work together. In their editorial, Salvage and Smith re-kindled the debate on how best to combine the talents and commitment of nurses and doctors to improve patient services.[62] They argued that dispelling any resentment between doctors and nurses is an important step and that disputes about their roles should be replaced with a discussion of how to make the best use of the wealth of different skills that the different health professionals bring to primary care.

A number of trials of nursing in primary care were also reported in this theme issue. An RCT by Shum and colleagues of 1815 patients who requested same day appointments showed that patients were more satisfied with nurse consultations compared to doctor consultations with mean (standard deviation SD) satisfaction scores of 78.6 (16.0) out of 100 points versus 76.4 (17.8) for doctors (95% CI for the difference between means: -0.38 to 4.07)[63]. In this study, the nurse consultations were slightly longer (10 minutes compared to 8 minutes for doctors), and nurses and doctors wrote prescriptions for a similar number of patients. This study illustrates that practice nurses can offer an

effective service, although the results are limited to patients who presented with acute minor illness. A trial conducted by Kinnersley and colleagues of nurse practitioners reported in the same issue of the BMJ supported these results.[64]

Nurse-led care in hypertension

Although nurse-led care appears to be effective in many areas of primary care, there is little evidence that nurse-led care is effective in the management of hypertension. Oakeshott and colleagues reviewed 10 studies of nurse-led management of high blood pressure, which were all of generally high methodological quality in terms of randomisation, blinding, and reports of losses to follow-up.[65] This review found that nurse-led hypertension management and cardiovascular health promotion without a change in prescribing had little or no effect on blood pressure. Only one of the included trials, in which patients with blood pressure levels above certain cut-off points were referred to their GPs for drug treatment, showed an important difference.[66] This review concluded that the most important advantages of nurse-led care included improved anti-hypertensive prescribing, better adherence to treatment and better follow-up due to rigorous application of national guidelines. The authors identified a need for randomised controlled trials based in primary care to further evaluate the effectiveness of nurse-led care by specially trained practice nurses in improving blood pressure control.

2.4 General concepts in adherence research

2.4.1 Introduction

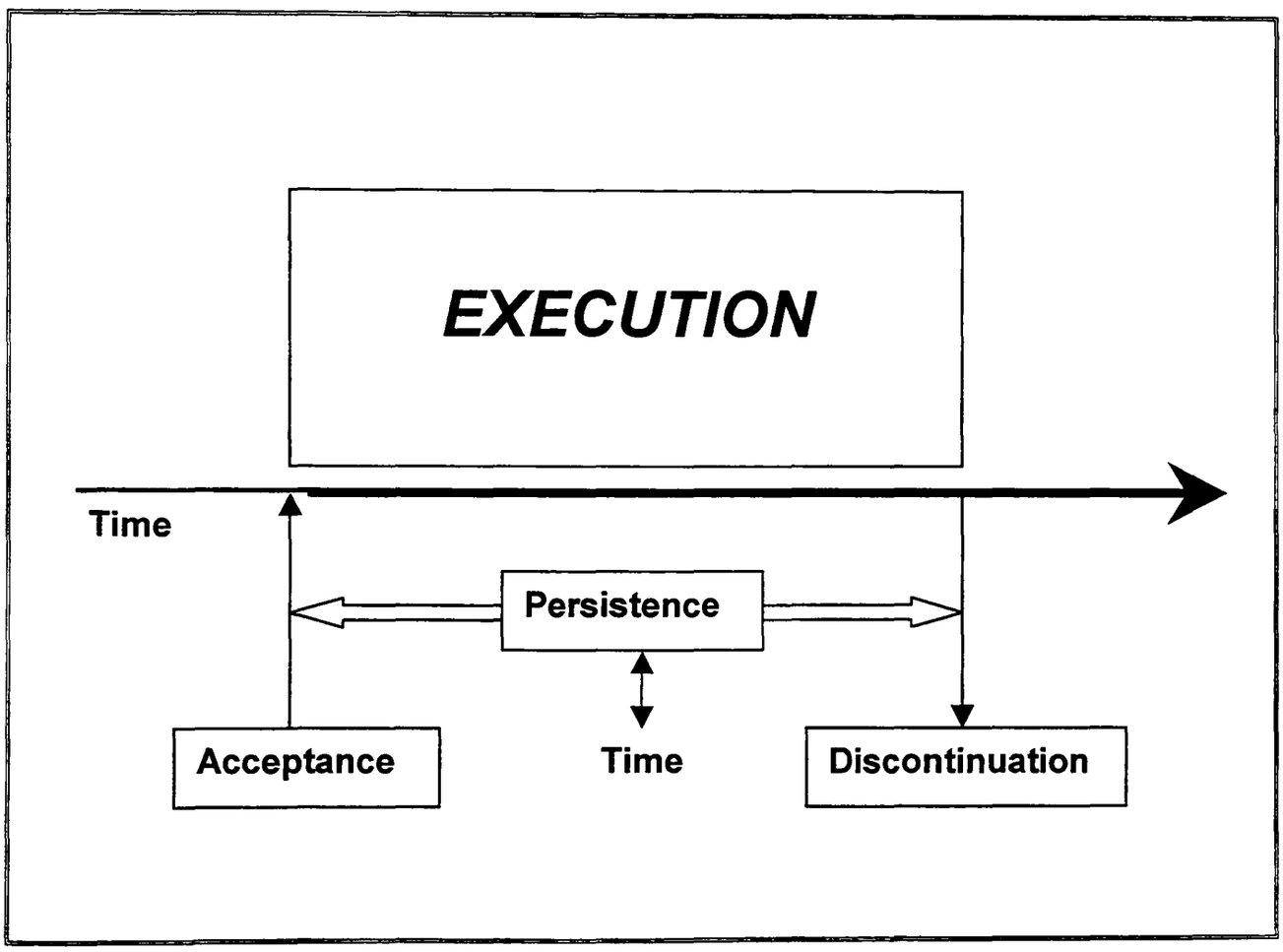
Therapeutic drugs are powerful tools of modern medicine, but the effect of medicines depends on the extent to which they are taken. The quality of a patient's execution of a prescribed pharmaceutical regimen has been a focus of research for many years and has led to a number of different terms such as compliance, adherence, concordance and persistence to describe this topic.[67] Different viewpoints, for example from a behavioural or therapeutic angle, may be partly responsible for this confusing array of terms. In addition, the ambiguity of terms is also due to the various methods used to compile accurate dosing histories of ambulatory patients.[67] Because particularly the terms *compliance* and *adherence* may exaggerate the health professionals' control over the process of taking medications, their correct definition and differentiation from the term *concordance* is the topic of an ongoing debate.[68,69]

It is easy for health professionals to see non-adherence as some form of deviant behaviour, but this view is unjustified.[70] Donovan & Blake took a rather cynical view of the term 'compliance' and argued that this concept is largely irrelevant to patients who carry out a 'cost-benefit' analysis of each treatment, weighing up the costs and risks of each treatment against any benefit that may result from the medication.[71] Although this view can be justified in cases of intentional non-adherence, it does not help to explain and understand the problem with non-intentional non-adherence.

2.4.2 Definition of terms

This section provides brief definitions of terms commonly used in ambulatory pharmacotherapy. An understanding of these and the different methods and definitions of dosing histories is essential for interpreting research in the field of adherence (see Figure 3)

Figure 3 Definitions in ambulatory pharmacotherapy



Acceptance or adoption

This is a dichotomous variable, describing whether the patient does or does not accept the recommended treatment after discussion of the treatment plan and agreeing to take

the proposed medication.[72] Whether a patient accepts the proposed treatment plan depends on various factors, including the patient's understanding of the diagnosis, the risks that are involved in taking or not taking the recommended regimen, and the role of the prescribed drug regimen. The phase starting with acceptance ends after the pharmacist dispenses the prescription to the patient and the patient takes the first dose.[72]

Execution

Execution is part of the patient's daily life and refers to the daily taking (or not-taking) of the prescribed dose at the prescribed time(s) every day[72]. This term describes a continuous variable, with a wide spectrum of patterns of deviation from the prescribed regimen, which may vary over time. The quality of execution can be described as patient compliance (see below).

Discontinuation

Although many treatments for chronic conditions are meant to be for life, many patients decide for a variety of reasons to discontinue with the prescribed treatment. Discontinuation is a term used to describe the time when a patient stops taking the prescribed medication regimen.

Adherence

Adherence is a useful overall term, which takes into account acceptance, execution and discontinuation of medical treatment. Poor adherence to medication can imply problems with any of the three terms persistence, compliance and concordance, which I define in the following paragraphs.

Persistence

The term persistence designates the length of time between acceptance and discontinuation of treatment. The crucial element inherent in this term is the time factor – that is, the duration of execution – unlike discontinuation, which is an event.

Caro and colleagues found a relationship between persistence with blood pressure lowering therapy and the initial drug prescribed in a large cohort study in Canada. [8] In a sample of 22,000 newly diagnosed and treated hypertensive patients, persistence at 12 months was generally poor and different for individual drugs, with 80% for diuretics,

85% for beta blockers, 86% for calcium channel blockers and 89% for ACE inhibitors ($p<0.001$). This study looked at different explanations for the results but failed to acknowledge whether a simple change in medication could have led to the stopping a particular drug. The authors also found that persistence with antihypertensive treatment decreased in the first six months after starting therapy and continued to decline for the following four years.[73] Only 78% of the newly diagnosed hypertensive patients continued with the therapy for one year, compared to 97% of the patients who had established hypertension and had taken blood pressure lowering medication for a minimum of 10 months ($p<0.001$). These results suggest that successfully passing the early therapeutic phase after initiation of treatment may be crucial for achieving long-term persistence.

Data for UK general practice indicate that discontinuation rates or changes after new prescribing of blood pressure lowering medication may be even higher. A retrospective analysis of 37,643 hypertensive patients on an automated database showed that discontinuation rates ranged between 40 and 50% for all four classes of antihypertensive drugs that were evaluated.[74] However, this study could not provide any information about the reasons why so many people discontinue treatment with antihypertensive medication.

Compliance

Compliance describes the quality of execution of the recommended drug regimen, mainly from a biomedical perspective. It can be defined as the degree of correspondence between the actual dosing history and the prescribed regimen.[75] This definition of compliance is useful for the analysis of compliance data, as it can take into account information about the timing and patterns of medication intake. 'Timing compliance', which I will in more detail define later, can, for example, be used in analysing and modelling its impact on drug concentrations, drug actions and clinical outcomes and has been used as the primary outcome for the RCT described in this thesis.

Although according to this definition compliance is a neutral term, it has been criticised as being problematic, as it may express an underlying ideology that assumes that patients ought to follow health professionals' instructions with a certain degree of deference.[76] Earlier definitions of adherence such as 'tending to follow medical recommendations', which are widely used in the adherence literature, are not meaningful.

Compliance also has an important time component, because drug actions depend on the dose and the time between doses. Every drug has a specific dose-response curve, which describes the rise and fall of the drug action or concentration after each dose. There are wide differences between drugs on how long their actions persist after a taken dose, and the dose-time response curves can also vary in shape. These curves can also help in determining the extent to which patients need to adhere to a prescribed regimen in order to achieve the desired effect.

Concordance

The term concordance was introduced recently and draws on research providing new insights into the relationship between prescriber and patients, taking a more patient-centred approach.[13] Every clinical encounter between health professional and patient has to take into account the health beliefs of both patient and prescriber.[77] It should be the task of the patient to inform the health professional of his or her health beliefs, and the health professional's task is to enable the patient to do this. This aims to form a 'therapeutic alliance' to help the patient with making a more informed choice about the medical diagnosis and its management.[77] This model has been named concordance, which, in contrast to the term compliance, aims to describe an agreement between patient and health care professional about the whole process of medication taking.[13,78,79] However, it is important to acknowledge that the term concordance does not aim to replace the other terms mentioned above. It focuses more on what actually happens during the consultation between patient and prescriber rather than describing the extent of medication taking.

2.4.3 Issues around adherence related terms

Adherence, compliance and concordance are often used interchangeably when studying health behaviour change, but their meanings are in fact different, particularly in the context of controlled clinical trials examining interventions aimed at improving adherence. According to Brawley & Culos-Reed, the term adherence takes into account that people choose to take their medicines, have control over their use, and develop an agreement with health care professionals about their management.[80] In their opinion, compliance implies obeying behaviour and that people follow instructions and prescriptions assigned by a health care provider. The main difference between the terms adherence and compliance is on a motivational level. The former implies a more active

role of patients in their management, whereas the latter is characterised by more passive behaviour. Unfortunately, as a result of trying to apply 'political correctness' the term concordance has occasionally, and not always appropriately, replaced the terms compliance or adherence.[69] The current and so far still open debate over these terms is perhaps a gentle reminder that the relationship between patient and health professional is also often based on poor communication and misunderstandings.

A further unhelpful distinction is the classification of patients into adherers and non-adherers, which implies an all-or-nothing behaviour.[4] Instead, adherence should be based on the specific level of adherence that is required to achieve a desired therapeutic response.[81]

For this thesis, I have chosen to use the term adherence, because of the motivational perspective associated with this term. Adherence is also the expression that is currently being used by the World Health Organisation.[2] Although adherence is often defined as above, that more traditional definition does require some modification, which should take into account cut-off points for specific diseases and therapeutic drug groups. Adherence is thus a useful overall term. Timing compliance, a specific term to describe the execution aspect of adherence, was the primary outcome for the trial described later in this thesis.

2.4.4 Measuring adherence

No single method of measuring adherence is suitable for all settings or outcomes.[82,83] Regarding assessment strategies for any outcome, assessment of adherence must demonstrate validity and reliability. According to Pullar & Feely, the ideal measurement of adherence should: a) be usable over a prolonged period, b) be unobtrusive, c) be non-invasive, d) be practicable and cheap, e) yield immediate results, and f) not be open to manipulation.[84] Based on these stringent criteria, the objective measurement of adherence is difficult and poses a major problem for researchers and clinicians alike. What follows is a brief description of the most commonly used methods of measuring adherence, starting from more traditional methods and then moving on to more recent advances. These can be separated into direct methods, which prove ingestion of the drug (such as the measurement of drug metabolites in plasma), or indirect methods, which do not prove ingestion of the drug (such as self-report or electronic monitoring).

Prescribing data

Data on medication prescriptions can be used as a simple method to assess primary non-adherence, that is, the rate of patient who do not redeem their prescriptions. Although this method detects non-adherence in those people who have not redeemed their prescription, it does not provide much useful information about those people who have had their medication dispensed to them.

Beardon and colleagues performed an observational study on 4854 patients and found that 14.5% of the study participants did not redeem their prescriptions during the study period (11.5% men and 16.3% women).[85] Their results also showed that non-redemption was associated with age, sex, general practitioner, exemption status, and on which day of the week the prescription was written. The rates of non-redemption were particularly high for cardiovascular drugs (52% for men and 57% for women).

Self-report or patient interview

Morisky and colleagues conducted a study on concurrent and predictive validity of a self-reported structured four-point adherence measure in 400 patients in two outpatient clinics of a large teaching hospital.[86] They found that 75% of the patients who scored high on the four-item scale at year two had controlled blood pressure at year five, compared with 47 per cent of those participants scoring low ($p<0.01$). However, these results have to be interpreted with caution, as adherence was not validated using another method of measuring adherence such as electronic monitoring, which was not widely available at the time of the study.

Despite being relatively easy to conduct, patient self-report unfortunately cannot provide detailed information about the execution of the drug regimen and is therefore of limited value if high quality data about adherence are required. However, when trying to assess adherence in the medical interview, a non-accusatory, open-ended and matter-of-fact approach is most likely to be of value.[87] There is also evidence to suggest that it is easier to change the self-report of adherence rather than adherence itself.[88]

Although it has its limitations, adherence self-report is the easiest method to employ in clinical practice, because it is inexpensive, quick and non-invasive. For this reason adherence self-assessment tools continue to be developed and evaluated. More recent studies validated these tools using electronic medication monitors (MEMS®) with promising results.[89,90] I will discuss the latest research in this area in more detail in the

background section of Chapter 6, which describes a validation study of an adherence self-assessment tool.

Pill counts

Using this method, the pill bottle contains more tablets than needed for the course of treatment. At the end of the course the pill bottle is recovered, and the remaining number of pills is used to calculate pill consumption. Pill counts give numerical values of doubtful objectivity and precision. It is easy for patients to discard or hoard untaken doses to create the impression of good adherence with the prescribed drug regimen – an occurrence that has been widely documented.[83,91-94] In an ambulatory hypertensive drug trial, pill counts misclassified adherent subjects in 22% of visits compared to electronic monitoring.[95] In this study, adherence was almost perfect with 92% and 99% for both treatment groups; electronic monitoring confirmed that fewer than half of the openings occurred at the prescribed interval of 12 ± 2 hours. Cramer and colleagues found in a relatively small study of 24 study participants with epilepsy that pill counts overestimated adherence increasingly as adherence with the prescribed regimen declined.[93] The study team used electronic monitoring in the comparison group and discovered that neither drug serum concentrations nor pill counts would have identified the number of skipped doses that were revealed through electronic monitoring. Guerrero and colleagues assessed medication taking in 19 ambulatory hypertensive patients, using both pill counts and electronic monitoring, and confirmed these findings. In their study, 51% of the monitored periods between two visits displayed 80% or more of vial openings within the desirable range of 24 ± 6 hours. In contrast, pill counts detected only 2% of these suboptimal dosing intervals. Despite this being a small study, it adds to the evidence that pill counts tend to overestimate adherence substantially.

Clinical outcome

If no other method of measuring adherence is available or appropriate, clinical measures (such as heart rate in the use of beta blockers or direct therapeutic response) in addition to non-threatening approaches for asking open questions about medication adherence may have some value in helping the clinician to decide whether a patient is taking medication as prescribed.[96] Positive information about non-adherence is helpful, but false negative reporting is common.[93]

Haynes and colleagues compared clinical assessments with pill counts in 134 newly treated hypertensive steel workers during the first six months of their treatment with blood pressure lowering medication.[97] In this study, participants overestimated adherence by an average of 17%, but 90% of those who admitted to not taking their medicines as prescribed were indeed found to be non-adherent.

Clinical measures of adherence largely depend on the condition being studied and assume a cause and effect relationship, which is rarely applicable. They also have to take into account the stage of the development of the disease and knowledge about the efficacy of the drug that is being administered, as well as the clinical skills of the practitioner performing the outcome measurement. If a medication is 'forgiving', that is, has a long duration of action, then incomplete adherence may not influence the effectiveness of the medication.

Pharmacological indicators

By adding a low dose of another compound to the medication being studied, this can be used as a pharmacological indicator if it has an appropriate plasma half life and elimination curve. It is also important that this substance is easy to measure in blood or, preferably, urine. Although this technique is relatively accurate and reproducible,[4] there is a problem relating to the sampling. This method only allows an estimate of adherence for a certain time before the assessment, often not more than one or two days prior to sampling, which is only a small fraction of typical treatment times. Blood sampling will mostly occur at the time of scheduled visits, but in patients who do not fully adhere to the treatment regimen the several days prior to the scheduled visit are often a period of particularly good adherence, which is also called 'white-coat compliance'.[98,99] The use of this method of measuring adherence is further limited because it is invasive, often requires explicit patient consent, needs special laboratory equipment and personnel and is prone to intra- and inter-patient variations. This method is, therefore, often not appropriate for assessing adherence in research or clinical practice.

Monitoring the primary therapeutic agent

The plasma concentration of the primary therapeutic drug in question can also be measured in many instances, but this method always depends on the pharmacokinetics, that is, the uptake, distribution and elimination of the prescribed drug and accurate data on the timing of the last dose. However, pharmacokinetics depend on numerous other

factors, which include gastric acidity, total body fat, or renal function. It is also impossible to estimate blood levels between measurements using this method, which makes it therefore unsuitable for use in the primary care setting. This method also has a limited value in that it only provides data for the days preceding the blood test.

Electronic monitoring

Micro-electronic methods have greatly advanced over the past decades and allow recordings of the timing and frequency of drug ingestion, which make them the only method to provide data on drug taking patterns. Devices are now available for tablets, capsules in blister packs, eye drops, or inhaled aerosol medication, which record the opening or activation of the medication container.[4]

One of these devices used for tablets is the Medication Event Monitoring System (MEMS®). The MEMS® uses standard tablet containers, but the lids have a spring-loaded mechanism which is connected to a microprocessor, recording the time and date of opening. Current processors can record about 2000 openings and have a shelf life of up to three years. Data can be downloaded onto a personal computer with a so-called downloading port, and data can be displayed graphically using the PowerView® software.

A great advantage of this method is that it can provide detailed data on the execution, which includes information on dosing patterns such as day-to-day variability in medication taking, a rise in adherence in the days preceding the consultation ('white coat compliance'), an absence of dosing during weekends, or lapses in medication taking ('drug holidays'), which can occur at any time.[98,100] It allows the calculation of unique adherence variables such as taking compliance, correct dosing, timing compliance and therapeutic coverage (these terms will be defined in more detail later) and is the only method of detecting 'drug holidays'.

There are, however, limitations to electronic monitoring. First, there is no guarantee an opening of the medication container is followed by ingestion of the correct dose. Second, the recorded opening of the monitor does not indicate how many drug doses were removed. However, it is more difficult to falsify than any of the other methods, because a patient has to open the medication monitor every day at the correct time to be

classified as adherent. Third, patients may prefer their drugs being dispensed in a multi-dose organiser. Fourth, the health professional handing over the monitor must accurately record the time when the monitor was handed over to the patient and when it was retrieved, as only between those times are all the recorded openings and closures of the monitor attributable to the patient.[101] Errors of a day or two in long-term drug use will hardly have any consequences, but in the investigation of acute and short-term illness, small errors can pose major problems for data interpretation. Patient feedback is therefore required to assess whether the devices were used appropriately at all times. Although bias may occur by patients being aware of being monitored and therefore changing their behaviour, any so-called reactivity bias is usually short-lived, with patients returning to their regular self-medication behaviour patterns after about four weeks.[98] Although electronic monitoring is currently regarded as the method which is closest to a 'gold standard' in measuring adherence,[101] it has so far been used mainly as a research tool due to its relatively high cost.

2.4.5 Distinction between non-adherence and non-response

A reliable dosing history is necessary to provide the basis of an objective assessment of patient adherence to help distinguish between non-adherence and non-response relating to pharmacological therapy.[102,103] Pharmacological non-response is likely if good adherence can be demonstrated, and non-response in the presence of gross non-adherence is convincing that non-adherence is a sufficient, if not necessary, cause for the lack of clinical response. There is, however, an intermediate zone where it is useful to know how much adherence is required to achieve the desired clinical effect, which is a particularly important question in patients who are prescribed long-acting drugs.[101]

The relationship between adherence and treatment response is not simple and can influence the extent to which health professionals and patients perceive the importance of complete adherence.[88] A recent 'prospective case control study' with 110 consecutive medical outpatients with hypertension who have taken at least two antihypertensive drugs for at least four weeks claimed that non adherence to blood pressure lowering medication was not more common in treatment resistant high blood pressure than in patients who responded to treatment.[104] However, the authors did not take side effects or pharmacological aspects of the medication into consideration. The study was too short and too small to reach any firm conclusions about the relationship between adherence and blood pressure control.[105]

2.4.6 Presentation of adherence data

Electronic medication monitoring can provide detailed data on adherence and can take into account not only the number of doses taken, but also the number of days during which the correct number of doses was taken. Different definitions have emerged, which can be expressed in percentages:[67,106]

1. Based on dosing: the number of doses recorded as taken, divided by the number of days of treatment multiplied by the number of doses prescribed during a monitored period
2. Based on number of days with correct dosing: the number of days during which the correct number of doses were taken, divided by the number of days of intended treatment
3. Based on the interval between doses: the number of correct intervals between doses divided by the total number of intervals between prescribed regimens based on a defined threshold, also known as 'therapeutic coverage'
4. Based on the interval between doses: treatment time during which the intervals between doses correspond, within predefined limits, to the prescribed interval (timing compliance)
5. Based on a pharmacodynamic (PD) and pharmacokinetic (PK) model: time that simulated concentrations, via a robust PK-PD model, of drug in plasma and drug actions fell within a defined therapeutic range

It is worth noting that time has a central role in all but the first of these expressions of compliance data.

2.4.7 Reasons for non-adherence

There are a number of reasons why patients may not take their medication as prescribed, either intentionally or involuntarily (see Figure 4). [107] All these factors may be responsible for non-adherence either alone or in combination, which adds to the complexity in this field. Non-adherence is universal and not connected with any specific demographic or socio-economic factor.[108] It is encountered both in symptomatic diseases such as epilepsy or asthma [109,110]as well as asymptomatic diseases including hypertension and hyperlipidaemia,[81,111,112] and even serious illness such as infection with the human immunodeficiency virus (HIV).[113]

Figure 4 Common reasons for non-adherence

Condition-related

- Disease severity
- Symptoms
- Rate of progress

Drug-associated

- Appropriateness of the prescription
- Side effects
- Number of daily doses
- Drug presentation/formulation
- Number of drugs prescribed concurrently
- Duration of treatment

Physician related

- Communication
- Information
- follow-up

Patient related

- Forgetfulness
- Mistakes
- Beliefs
- External factors
- Environment (e.g. home, work)

Adapted from: Sackett & Haynes. Compliance with therapeutic regimens. Baltimore & London: The Johns Hopkins University Press, 1976.

Unintentional lack of adherence may, for example, simply be the result of forgetfulness due to a busy lifestyle, lack of memory associated with dementia, failing to understand the prescriber's directions, failure to understand the importance of long-term maintenance therapy, polypharmacy, or a complex dosage regimen of more than one dose per day. With regard to the number of daily doses, a recent review article by Claxton and colleagues found that the prescribed number of daily doses is inversely

related to medication adherence in a number of different therapeutic drug classes.[114] Only studies using electronic monitoring were included, and the pooled results showed that mean dose taking for a once daily regimen was 71% ± 17% (range 34 to 97%) and declined with an increasing number of daily doses with 51% ± 20% for a four times daily regimen ($p<0.001$).

Intentional poor adherence may be based on a rational decision not to take a medicine as prescribed. People have their own beliefs about health, illness and the use of medicines in general, which may sometimes be in contrast to those of health professionals.[115,116] These beliefs can be influenced by people's socio-cultural background, the knowledge about the disease and its management, the individual's perception of the risk of not taking the medicines, information from friends and relatives or the media, the relationship with the health professional or prescriber, dislike of side effects, fear of developing immunity, dislike of artificial chemicals, desire for autonomy, and many other behavioural or psychological determinants.[4]

A qualitative study nested within a pragmatic randomised controlled trial on non-adherence with physiotherapy in 20 patients with osteoarthritis of the knee highlighted the importance of understanding the reasons for non-adherence if health professionals want to provide supportive care.[117] The results of this study showed that adherence-related behaviour was complex and depended on issues around loyalty to the health care professionals, willingness to accommodate the treatment into daily life, the perceived severity of symptoms, attitudes to the illness, previous experiences of patients' diseases and the belief that the physical treatment was effective in improving pain and other unwanted symptoms.

Social factors such as a weak social support network, lack of transportation, social isolation, visual problems, or concerns about leaving the house also need to be taken into consideration.[118]

2.4.8 Lay views of medicines

Whether people take prescribed medicines is not only informed by beliefs about medicines but also by beliefs about the medical condition, which the medication intends to prevent or treat.[115,119] A number of qualitative studies have been conducted in this field, which have shown that people have specific beliefs about medication in general[116,120] and about hypertension in particular.[121]

Despite the large number of studies on adherence in hypertension, there is still little understanding about how patients themselves perceive blood pressure lowering treatment and about possible variations between different ethnic groups.[122] Morgan described in a qualitative study based in 15 London general practices how 30 White and 30 Afro-Carribean hypertensive patients were aware of and often commented on the ambivalent status of being "under the doctor" for blood pressure but not "sick" as such.[122] Respondents in this study were generally well aware of the fact that high blood pressure could lead to an increased risk of death, heart attack, and stroke. Major concerns in both groups were worries about possible "side effects", that is, drug adverse effects of an unwanted or serious nature, in the future. Another important reason for people's dislike of medicines was a perceived risk of becoming "addicted" to the drugs. Whether people stop taking their tablets for these reasons or become less adherent will depend on the strength of these beliefs, patients' assessments of the seriousness of their condition, and the perceived benefits of their medication.

Horne and colleagues have recently developed a questionnaire-based method for assessing beliefs about specific and general medication, the 'Beliefs about Medicines Questionnaire'.[123] The core themes relating to the prescribed medication for the patients were beliefs about medicines helping to maintain health and concerns about the medication.

2.4.9 Psychological concepts of health-related behaviour

To increase adherence to medication effectively, interventions have to help patients change their behaviour. A number of different models and theories have been used to predict, explain and understand adherence.[80] Theories of health behaviour commonly used in adherence research are the self-regulatory model of illness behaviour, the self-efficacy/social cognitive theory,[124] the relapse prevention model,[125] and the transtheoretical model.[80,126] Most of the models used in adherence research attempt to explain the processes that are inherent in behaviour change, and all these theories assume that people are able to make goal-directed rational decisions. However, it is important to recognise that many of these models, such as the health belief model or the self-efficacy theory, are relatively simplistic and have often failed to provide an adequate explanation of adherence related behaviour.

This section looks at some of the differences between these models and theories and discusses the rationale behind why I chose the self-regulatory model as a theoretical basis for this thesis.

Social cognitive theory

This theory, formed by Bandura in 1986, used a social-cognitive viewpoint to analyse and understand human cognitions, actions, motivations and related emotions in within a broad theoretical framework.[124] This model not only discusses learning, but it also includes other issues such as psychosocial factors that cannot be explained by social learning theory. A central element of this theory is an assumed interaction between the person, the behaviour and the environment, with each of these factors helping to determine the others. This does not mean that all these factors influence each other equally or simultaneously, but they are all important to understand behaviour.[80,124] In relation to adherence, this theory recognises that people are not passive individuals open to any kind of intervention.

Relapse prevention model

The relapse prevention model, as well as the transtheoretical model covered next, is a fairly recent and relatively complex model.[125] The main idea of this model is that the success of an individual in maintaining a new behaviour, such as adhering to a medication regimen depends on the ability to cope with a relapse to a behaviour that is less desirable, which might include not taking medication or taking it irregularly. This model aims to help people develop skills in self-awareness to differentiate a lapse, which might be accompanied by warning signs of changing back to an undesirable behaviour, from a complete relapse, which is characterised by a complete reversion to the undesirable behaviour. By using this model, individuals are also taught to use skills in self-regulation to cope with any lapses effectively in order to avoid complete relapses.

Transtheoretical model

This model has become popular among health care practitioners despite relatively little objective research support.[80,126] It is based on the assumption that when attempting to change health behaviour people pass through five stages on the way from contemplating a health behaviour change to maintaining the desired behaviour. These stages include a

precontemplation phase followed by contemplation of the envisaged behaviour, preparation for change, eventual action and then maintenance of the desired behaviour. This model appears to be appealing due to its intuitive approach to changing health behaviour, because in each stage individuals show a certain readiness for change. Although people usually proceed through these stages in sequential order, they can advance and regress in a spiral-like fashion before maintaining a newly acquired health behaviour.[126]

Health belief model

According to Janz & Becker, health behaviour is influenced by four main beliefs, which include: a) the perceived risk of developing a particular disease or condition, b) the perceived seriousness of the health threat, c) the perceived benefit associated with taking preventive action, and d) the perceived barriers associated with taking preventive action (for example, disadvantages, costs, discomfort).[127] In relation to adherence, higher adherence would occur in individuals who see their condition as being serious, who feel that they are at risk and believe that the benefits of adhering to the treatment regimen outweigh the costs.

This model is very intuitive and has become popular in the adherence literature to help explain non-adherent behaviour. According to this theory, non-adherent people do not perceive themselves as ill, are less inclined to take into account the benefits that may result from the prescribed treatment regimen. However, based on work by Haynes and collagues, the assessment of patients' health beliefs is not always helpful, as there are many other reasons for non-adherence than those based on patients' perceptions (see Figure 4).

Self-regulatory model of illness behaviour

This model was developed by Leventhal and is based on models of problem-solving.[128-130] It suggests that individuals deal with illness or medical symptoms in the same way as they deal with other problems. Assuming a health-related problem such as a new illness or having to take medicines for the first time, an individual will be motivated to solve the problem and to re-establish the preceding state of normality.

The self-regulatory model consists of three stages. Stage one includes interpretation of the problem and assigning a meaning to it by taking into account the individual's illness cognitions. This stage is followed by developing and identifying suitable coping

strategies in stage two. The two broad coping strategies usually employed are approach coping, which might include the taking of prescribed pills, or avoidance coping characterised by denial or wishful thinking. The third stage of the self-regulatory model consists of an appraisal and evaluation of the strategy, during which an individual decides about continuing with the strategy or whether to try a different one.

Rationale for using the self-regulatory model for this thesis

Despite useful models being available for studying adherence-related behaviour, there is so far no convincing evidence to endorse a single model.[80] I have chosen the self-regulatory model as the main theoretical basis for this thesis, because people have beliefs about illness in a similar way as they have about health. Evidence from mainly qualitative research shows that people have a variety of beliefs about their illness as well as its treatment with medication.[13,116] The particular strength of the self-regulatory model is that it takes into account individual symptom perception, emotional responses to a health threat such as fear or depression, coping strategies including approach and avoidance, and finally an appraisal as to whether the coping strategy was effective. Because traditionally many consultations in primary care use a problem-solving approach, this appeared to be the right model to describe how patients make sense of their illness and their medication management. The novel and distinguishing features of this model are that patients' assessment of their treatment plays a central role in it and that it recognises that emotional as well as cognitive processes are involved in making decisions as to whether or not to take prescribed medication.[131] Based on this model we designed a nurse-led adherence support intervention, which aimed to identify and address individual medication problems together with each patient. The way this model assisted in the design of the intervention is described in section 5.9.2.

2.4.10 Problems and consequences of non-adherence

It is difficult to make general statements about the medical and economic consequences of variation in dose-timing, as these are specific to the particular medicine being used, the disease in question, the severity or extent of the medical condition as well as the type and influence of any significant co-morbidity.[132]

Clinical consequences

The formulation and medication regimen also play an important role in determining the peaks, troughs, and the rates of a rise and fall in drug blood concentration.[133] These factors, which can be influenced by the uptake, distribution and elimination of the drug in question, can affect the margin of error in dose-timing and reduce the risk of rate-dependent adverse or rebound effects (an example of which would be a higher than expected transient rise in blood pressure after suddenly stopping an antihypertensive drug).[134] The term 'forgiving' is used to describe medicines that have a substantial margin of error in dose-timing.[132] For example, the original oral contraceptives had high oestrogen doses and were relatively forgiving in terms of missed doses.[135] Modern combined oral contraceptives, and the progesteron-only pill in particular, are much less forgiving. They carry a warning in the UK that if there is a delay in taking the pill by more than 12 hours, barrier contraception should be used for the next 7 days.[136] Oral contraceptives are more or less the only type of medicine for which explicit instructions are being issued on what to do if a dose is missed by a certain amount of time.[132]

Economics of non-adherence

Non-adherence may cause additional health care costs in a number of ways. In terms of clinical outcomes, non-adherence has been shown to be associated with increased morbidity and mortality in chronic disease.[137] There is some evidence that non-adherence is likely to be associated with costly hospitalisations and visits to emergency departments. An economic evaluation carried out in the United States estimates that about 5% of all hospital admissions are linked to poor adherence, leading to 1.9 million admissions annually at a cost of several billion dollars.[138]

To evaluate the evidence on the economic effects of non-adherence, Cleemput and colleagues conducted a review of 18 studies that attempted to calculate costs relating to non-adherence.[139] Perhaps not surprisingly, they found similar problems as the general adherence literature: many studies used diverse designs, defined and measured adherence inaccurately, and used invalid methods for calculating economic costs. The investigators did not find any studies from before 1982, which indicates how relatively new this research topic is. The review shows that the standard principles of good economic evaluation have rarely been applied in the adherence literature to date. The authors therefore concluded that more research of higher quality is needed to assess the

impact of non-compliance and the cost-effectiveness of interventions to improve adherence.

Hughes and colleagues provided recommendations for taking non-adherence into account in pharmaco-economic evaluations, which include consideration of the influence of premature drug discontinuation, the frequency of drug holidays, modelling consequences for chronic conditions, therapeutic coverage, stating any assumptions made and performing sensitivity analyses for adherence level and the outcomes associated with each level.[140]

2.4.11 Involving patients in their management

Medical models have in the past been formulated that see the patient as a passive recipient of medical care. These have been replaced by models that include the patients' values and preferences in the treatment decision-making process. This is particularly important in the field of adherence where patients should be encouraged to participate in decisions in order to gain maximum benefits for themselves.[141]

The concept of patient centred care

Patient centred care has received more importance in recent years. Although the term 'patient centeredness' is widely used, it remains a little understood concept in medical practice.[142] The relationship between health professionals and patients is complex, and a partnership between the two can take different forms.[143] A common misconception, however, appears to be that patient centeredness means sharing every piece of information and all decisions.[144] The correct meaning of the term encompasses the patient's desire to share information and decisions and for the health professional to respond appropriately.[142] Involving patients in the management of their medical conditions is important for good quality health care, particularly relating to the problem of intentional non-adherence.[145] Most people like more information about their diseases and the different treatment options available.[71,146] Patients in primary care also appear to want a patient centred approach with an emphasis on communication, partnership, and health promotion, as a questionnaire study by Little and colleagues with 865 patients in three general practices showed.[147] This study identified five components of patients' perceptions, which included communication and partnership, personal relationship, health promotion, positive approach to diagnosis and prognosis, and interest in the effect on life, each of which was found to predict different consultation outcomes.[148]

Patients make decisions about their treatment all the time, but often based on incomplete or false knowledge about their drugs, adverse effects and the most effective way to take them. The provision of simple information therefore could help them to make more informed decisions and assist with choices that fit into their current lifestyle.[149,150] Elwyn and colleagues argued in a recent discussion paper that the part of the consultation where decisions are made and future management is agreed has been neglected at a time when the development of communication skills has focused on establishing patient agendas at the beginning of the consultation.[151] They conclude that primary care practitioners are placed in an ideal position to share decisions with patients, but that this process will require, among other things, more time in the consultation. However, involving patients in health care decision also needs a willingness of patients to accept greater responsibility for choosing between alternative management strategies and for the resulting outcomes of the treatment.[145]

Other models have been used to describe treatment decision-making which include the paternalistic model, the informed model and the shared model.[144] The paternalistic model is characterised by the patient passively accepting the authority of the health professional. In the informed model, a partnership between patient and practitioner is formed, but information transfer is the only main responsibility of the professional. Only in the shared model do health professional and patient interact at any stage of the decision-making process at any time. In day-to-day medical practice, a combination of these models is likely to be employed, with varying emphasis on the different models, which may be adjusted to the needs of individual patients.[144]

Characteristics of shared decision-making

Different models of shared decision-making have been developed. One of these has four characteristics, which include: a) both the patient and the health professional are involved, b) both parties share information, c) both parties take steps to build a consensus about the preferred treatment and d) and agreement is reached on the treatment which is to be implemented.[152]

Using this model, a qualitative study by Stephenson and colleagues of 62 patients and 20 doctors showed little evidence that doctors and patients participate during the consultation in this way. Even the first two of the above characteristics were not generally present in the consultations that were studied, so there was no basis on which to base consensus decisions on the preferred treatment.[153]

Another study by Britten and colleagues investigated misunderstandings between patients and doctors that have potential or actual adverse consequences for taking medication.[154] This study, conducted with 20 general practitioners and 35 consulting patients in the West Midlands and South East England, identified 14 categories of misunderstandings, which related to patient information unknown to the doctor, doctor information unknown to the patient, conflicting information, disagreement about the attribution of adverse effects, failure of communication about the doctor's decision, and relationship factors. All of these factors were related to potential or actual outcomes such as non-adherence. This study highlighted the importance of patient participation in the consultation and subsequent decision-making.

Providing risk information for patients

Discussion of risk is an important element of the clinical consultation, but it can be difficult for patients to understand risk and recall information relating to risk.[155] Clinicians often use quantitative information such as relative risks or percentages, whereas many lay people may code information qualitatively.[156] How an individual perceives language or statistics used by a health professional depends on various factors, which among other things include the importance placed on an adverse event.[155]

It is important to remember that patients' understanding of risk can be different from that of health professionals. Guidance from the European Union recommends the qualitative description for five risk bands ranging from very rare (risk <0.01%) to very common (>10%).[157]

A study by Misselbrook & Armstrong pointed out the powerful effect that occurs when information is presented in different ways.[158] They found in a postal questionnaire study with 102 hypertensive patients and 207 matched non-hypertensive patients in a UK general practice that different ways of presenting risk to patients produced substantially different decisions among patients as to whether or not to agree to medical treatment. Of 89% who responded, 92% would accept medication based on information about relative risks (75% using absolute risk model, 68% using a number needed to treat model, and 44% with a personal probability of benefit model). However, this study is likely to be of limited generalisability, because it only recruited patients from one general practice.

Shared decision-making in hypertension

Decision aids are health care interventions to help people with making specific and deliberate choices among different options, which may include maintaining the status quo. This also includes providing all the relevant information desired by patients on the different options and the health outcomes that a relevant to people's health. Various decision aids have been developed that have the potential to achieve more informed decision-making in the general practice consultation.

A systematic review by O'Connor and colleagues found that decision aids are superior to usual care interventions in improving knowledge and realistic expectations of the benefits and harms of options and lowering decisional conflict, but they have little effect on anxiety or satisfaction with the decision-making process.[159] The authors also concluded that the effects of decision aids on medication adherence and health outcomes require further studies.

In their review article, Montgomery and Fahey highlighted the difficulties and challenges of shared decision-making if patients and clinicians do not agree in their preferences for different treatment options.[160] They found that differences in treatment preferences exist between patients and health professionals in cardiovascular disease and other specialties. For example, McAlister and colleagues investigated the treatment thresholds of family physicians and hypertensive patients for mild, uncomplicated hypertension in Canada. They found that patients were less likely to want antihypertensive medication than physicians, particularly in case of low baseline cardiovascular risk (e.g. 68% versus 92% for a five year cardiovascular risk of 5%, $p<0.001$).[161]

Montgomery and colleagues also conducted an observational study that aimed to investigate the impact of patient preferences on treatment recommendations for hypertension using individual decision analysis in 52 hypertensive patients.[162] The study results showed that individual patient preferences had a substantial impact on the proportion of patients for whom treatment with medication would be recommended. There was marked disagreement between the results from the decision analysis and the recommendations, resulting in kappa values of 0.18 or less. They found no difference between the outcome of the decision analysis and adherence to blood pressure lowering medication ($p=0.5$). However, this finding has to be interpreted with caution due to the limited value of repeat prescribing in measuring adherence.

Measuring patient involvement in decision-making

To date, no generally accepted measurement instrument exists that helps with the measurement of patient involvement in decision-making, although several instruments have been developed, as described in a systematic review by Elwyn and colleagues.[163] However, none of these instruments have been specifically developed for the purpose of measuring patient involvement in clinical consultations.

Promoting patient centred care in clinical consultations

A Cochrane systematic review of interventions for providers to promote a patient-centred approach in clinical consultations included 17 studies, which displayed considerable heterogeneity between the interventions, the health problems on which these interventions focused, and the outcomes assessed.[164] However, there was some evidence that the interventions assessed in this review may increase the patient centredness of care, but there was mixed evidence on the effect on patients' health care behaviours or health outcomes. Because there is currently no 'gold standard' of assessing and defining patient centredness and in view of the heterogeneity between the included trials, these findings have to be interpreted with caution. However, this review highlighted that assessing the effects of increased patient-centredness on patient behaviour and health outcomes should be an important element of future studies.

Eastabrooks and colleagues conducted a systematic review of mainly randomised controlled trials on the effectiveness of decision aid in medical practice.[165] They reviewed 20 studies that met their inclusion criteria and found little evidence to suggest that structured decision support interventions help to influence treatment preferences or actual treatment decision and called for further research in this area.

In a qualitative study of 29 participants, Dowell & Hudson found that most patients 'test' a medicine before accepting it fully and that a frank discussion of this testing phase could help patients with adhering to their drug treatment.[166] However, the authors acknowledged that, for example in blood pressure lowering treatment, drugs can often be stopped without any immediate symptomatic consequences. A testing phase could, therefore, help with establishing the tolerability of a drug for individual patients.

Competencies required for informed shared decision-making

Towle and Godolphin identified and proposed competencies for informed shared decision-making that aim to provide a framework to be used in teaching, learning, clinical practice and research (Figure 5).[167]

Figure 5 Competencies for physicians for informed decision-making

1. Develop a partnership with the patient
2. Establish or review patients' preferences for information (such as amount or format)
3. Establish patients' preferences for their role in decision-making (such as risk taking and the degree of involvement of self and others) and the existence and nature of any uncertainty about the course of action to take
4. Ascertain and respond to patients' ideas, concerns, and expectations (e.g. about management options)
5. Identify choices (including ideas and information that patients may have) and evaluate the research evidence in relation to individual patients
6. Present (or direct patients to) evidence, taking into account the above competencies and help patients to reflect on and assess the impact of alternative decisions with regard to their values and lifestyle
7. Make or negotiate a decision in partnership with patients and resolve conflict
8. Agree an action plan and complete arrangements for follow-up
9. Informed decision-making may also involve a team of health professionals, others such as patients' families, and can differ across cultural, social and age groups

Adapted from Towle & Godolphin, BMJ 1999;319:766-771.[167]

2.4.12 Interventions for increasing adherence

It seems appropriate that when trying to increase adherence, health professionals' prejudices as well as patients' perceptions have to be taken into account, and strategies

for improvement have to include educating the practitioner as well as counselling individual patients.[70]

A number of systematic reviews have investigated the effect of interventions to increase adherence to medication in general (interventions to increase adherence to blood pressure lowering medication will be discussed separately – see Chapter 3).[2,12,168,169] Despite a wealth of studies in this field that examine the effects of educational, behavioural, or cognitive interventions in various chronic diseases, there have been mixed results. The main conclusion common to these reviews is that so far no single strategy can be recommended to improve adherence.

The most recent systematic review by McDonald and colleagues found 6568 citations and included 33 trials testing 39 different interventions.[12] Interventions were tested that included: a) patient education (oral and written material and programmed learning), b) improved communication including counselling (for example, compliance therapy, automated computer assisted monitoring by telephone, manual telephone follow-up or family interventions), c) improving the convenience of care through self-monitoring of blood pressure, d) reminders (for example, tailoring the regimen to daily habits, special reminder pill packaging, dose-dispensing units of medication and medication charts, appointment and prescription refill reminders) and e) reinforcement or rewards for both treatment success and improved adherence. The chronic conditions in question included hypertension, schizophrenia or acute psychosis, asthma and chronic obstructive pulmonary disease, depression, HIV infection, diabetes, rheumatoid arthritis, epilepsy, hyperlipidaemia, and cardiovascular disease. Forty-nine per cent of interventions tested (19 out of 39 interventions in 33 studies) showed statistically significant increases in medication adherence and 17 showed improvements in treatment outcomes. These results have to be interpreted with a certain degree of caution, because studies, populations, interventions and outcome measures were heterogeneous, making comparison of trials difficult. This review highlighted the need for further development of effective interventions, which should be rigorously assessed.

The World Health Organization (WHO) has also recognised poor adherence as an international problem and recently published a report with the title *Adherence to long-term therapies: evidence for action*.[2] Written by leading experts in adherence-related issues and targeted mainly at policy-makers and health managers, it aims to provide a critical review of what is known about adherence to long-term therapies. This WHO report delivers an overview of general adherence issues and reviews ways to improve

adherence in a variety of conditions, including asthma, cancer, depression, diabetes, epilepsy, HIV/AIDS, hypertension, tobacco smoking cessation and tuberculosis. The overall conclusions are that patients need to be supported and not blamed, and that patient-tailored interventions are required that use a multi-disciplinary approach. This report also emphasises the need for further research in this field due to the lack of high quality studies.

2.5 Adherence in hypertension

General issues around antihypertensive treatment

Treating hypertension in ambulatory patients is based on long-term oral medications that lower blood pressure and thereby delay or prevent cardiovascular morbidity and mortality. The management of hypertension, therefore, involves largely healthy individuals who are at increased risk of developing cardiovascular disease. The psychological concepts and models described above can be used to help explain risk behaviour as well as preventive or protective behaviour, but a number of additional issues need to be mentioned.

Epidemiology of non-adherence

Relatively little is known about the extent to which poor adherence is present in people taking antihypertensive medication. It is estimated that in the US poor adherence to therapy contributes to lack of blood pressure control in more than two thirds of people with treated hypertension.[27] For many years it was thought that poor adherence to blood pressure lowering medication is a result of inconvenient regimens and the side effects of non-specific drugs. Although more convenient regimens and specific drugs have been developed in recent years, studies conducted in Switzerland showed that lack of adherence to antihypertensive medication is still widespread.[172,173] To our knowledge, no reliable data exist on adherence levels in hypertension in the UK.

Barriers to adherence

There are several barriers to adherence with blood pressure lowering medication, some of which are similar for other chronic conditions, but others are specific to antihypertensive treatment. These barriers can interfere with full adherence at any time

of the therapeutic process.[107] Patients may resist being labelled as 'hypertensive' in the period after diagnosis and may therefore not keep regular appointments. They may not purchase or use prescribed medications, and side effects, which may be related to ingestion of each dose, could lead to stopping the therapy prematurely. Delayed adverse effects such as impotence or cough caused by particular drugs can lead to patient complaints or concealed non-adherence. Despite efforts to simplify the drug therapy in hypertension, this remains largely a process of choosing and adding drugs in an informed trial and error, based on each patient's individual circumstances and comorbidity (see Section 2.3.4). Stanton found in a study of 116 hypertensive patients at a health maintenance organisation in the US that greater expectancy for internal control over health and hypertension, greater knowledge about the medication regimen, and stronger social support were important determinants of adherence.[170] The study used self-report of adherence and kept appointments as outcome measures, and despite leading to helpful hypotheses, the results of this study have to be interpreted cautiously.

Benson & Britten conducted a study on why patients choose to take drug treatment for hypertension and exposed the ambivalence that some people feel about taking medication for chronic disease.[171] Reasons for not taking the medicines were often unrelated to the pharmacology of the drug itself, and any reservations about drugs developed in a way that made sense for individual patients (see Figure 6 and Figure 7). This study is another example showing the dilemma that many patients face when they try to resolve conflicting thoughts and ideas with regard to medical advice. Their work suggests that directly asking patients about their reservations, their reasons for taking the prescribed medication, and the balance between them, may help to improve the understanding between patients and health professionals.

Figure 6 Patients' reservations about medicines

Reservations about drugs in general

- Drugs are best avoided
- Drugs are unnatural or unsafe
- Drugs are perceived adversely because of previous experience
- Drugs are signifiers of ill health
- Patient brought up to avoid drugs
- Doctors prescribe drugs too readily

Reservations about antihypertensive drugs specifically

- Desire to discontinue using antihypertensives
- Preference for an alternative to drugs
- Patient questioned continued necessity
- Possible long term or hidden risks

Source: Benson & Britten, BMJ 2002;325:873-6.[171]

Figure 7 Patients' reasons to take antihypertensive drugs

Positive experiences with doctors

- Advice from doctors
- Trust in doctors
- Improved blood pressure readings

Perceived benefits of medication

- Achieving a good outcome
- Feeling better
- Gaining peace of mind

Pragmatic considerations

- Absence of a practical alternative to drugs
- Absence of symptoms to guide medicine use
- Drug use overshadowed by some other consideration

Source: Benson & Britten, BMJ 2002;325:873-6.[171]

Common medication errors

Based on data from electronic monitors, the most common errors with regard to adherence to antihypertensive medication include, in decreasing order of frequency: a) a delay in dosing, b) missing a single dose (for example, an interval of more than 48 hours in a once-daily dosing regimen), c) missing two successive doses (for example, an interval of more than 72 hours in a once daily regimen), and d) longer lapses in drug doses called 'drug holidays'.[72]

Recent developments

A study by Burnier and colleagues used electronic monitors to assist in the management of high blood pressure in subjects not responding to antihypertensive medication (refractory hypertension).[172] Forty-one participants with resistance to a three-drug regimen and a mean (± SD) blood pressure of 156/106 ± 23/11 mmHg were recruited to take part in a prospective non-randomised study and used electronic monitors for two months without any change in treatment. Using the medication monitors alone was associated with an improvement of blood pressure at two months (145/97 ± 20/15 (SD) mmHg, $p<0.01$). Because this study was small and did not have a control group, the results have to be interpreted with caution. However, this study introduced the new concept of using electronic monitoring as an intervention as well as an outcome measure.

In an earlier study among uncontrolled hypertensive patients in a Swiss primary care centre and a tertiary hypertension clinic, Bertholet and colleagues divided patients who after one to two months of electronic monitoring were at target blood pressure (group one), those who had markedly improved (group two) and those who remained unchanged (group three).[174] They found that electronic monitoring identified: a) potentially overtreated patients in group one, b) poor adherence to the prescribed regimen in all groups, and c) participants who clearly needed a change in treatment in group three. Despite this being another small and uncontrolled study, it highlighted the potential of electronic monitoring in differentiating between non-adherence and non-response, which still poses immense difficulties for health professionals in many specialties.

2.6 *Summary and implications for this project*

This chapter has provided an overview of current issues in adherence research in connection with the management of high blood pressure in the community. This review of the general hypertension and adherence literature highlights the complexity and challenges that any research in adherence faces, stressing the importance of using appropriate methods for measuring adherence that are as objective as possible. This led to including electronic monitoring for outcome measurement and 'timing compliance' as a more stringent definition of adherence in the RCT described later in this thesis. At the appropriate places in the following chapters I further justify why I have decided to use these methods to measure adherence.

3 How can we improve adherence to blood pressure lowering medication? A systematic review of RCTs

3.1 Introduction

While the previous chapter described and discussed the broader literature in the field of medication adherence in hypertension, this chapter focuses on interventions aiming to increase adherence. The main objective of this systematic review of RCTs was to determine the effectiveness of interventions to increase adherence to blood pressure lowering medication with the aim to inform our research question and the development of the intervention for the RCT described in chapters 5 and 6. It is based on a previous systematic review of detection, adherence and control of hypertension by Shah Ebrahim and was conducted collaboratively with Shah Ebrahim and Tom Fahey.[41]

My own contribution to this review included drafting the original protocol, performing the literature searches together with Margaret Burke, Trial Search Coordinator from the Cochrane Heart Group, screening titles and abstracts to select studies for the review, designing the original data extraction sheets, extracting the data, entering and summarising the data, and drafting the manuscripts. Although I was primarily responsible for all aspects of conducting this systematic review, I felt that I should use the plural 'we' rather than 'I' in this chapter to emphasise that this work was carried out collaboratively.

This systematic review is registered with the Cochrane Hypertension Group and was conducted according to guidelines laid out by the Cochrane Handbook and by Egger and colleagues.[175,176]

3.2 Overview and choice of methods used for this review

We chose to conduct a systematic review of RCTs, because studies using this design are likely to provide more reliable information about the effectiveness of health care interventions than other sources of evidence. Whereas the literature review presented in the previous chapter followed more traditional lines, the systematic review described here used a more comprehensive and unbiased search, aiming to identify all publications relevant to the research question. We aimed to achieve this by searching multiple databases and by investigating a variety of other sources to identify pertinent studies. We prepared a study protocol in advance, which was peer reviewed by editors

from the Cochrane Colloborative Review Group before the review was conducted. The protocol contained details about the review question, the *a priori* definition of our inclusion and exclusion criteria for RCTs to be included, our search strategy and plan for data collection and analysis.

3.3 Background

A variety of interventions aiming to improve adherence to antihypertensive medication have been evaluated in randomised controlled trials (RCTs), and four systematic reviews have tried to summarise the evidence in this field.[12,41,177,178] The searches in three of these reviews were limited to studies indexed only in MEDLINE,[41,177,178] thereby lacking in sensitivity and specificity,[179] and only included English language publications. None of these reviews could recommend any single approaches that increase adherence to blood pressure lowering medication. The most recent and more general review used a more comprehensive literature search and included six studies in hypertension.[12]

Since more trials in this area have emerged recently,[180-182] this prompted us to carry out a new systematic review of the literature to establish which types of interventions to increase adherence are most effective, using a more comprehensive search strategy and including foreign language publications. We also aimed to investigate and report the effect of individual interventions used in factorial trials. This review was initially registered with the Cochrane Heart Group, but during its conduct it was transferred to the Cochrane Hypertension Group for eventual inclusion in the Cochrane Library.

3.4 Methods

This section describes first our thoughts that led to the development of the research question. What follows is an account of the methods that we employed to conduct this systematic review. Section 3.4.1 contains the elements that formed the basis of the study protocol, whereas from section 3.4.2 onwards I report how the review was eventually conducted, including changes to the protocol and their justification.

3.4.1 Formulating the research question

A major objective in formulating the research question was to inform the literature search and the data collection process by: a) determining the criteria that we would use

to select appropriate studies for review and b) deciding what data should be abstracted from studies that met these selection criteria. We formulated the research question by specifying the key components, namely the types of studies, types of participants, types of interventions, and types of outcomes.

During this process we had to make decisions about how precisely to define these components, which directly affected the level of focus in the review. The aim was for the review to be sufficiently broad to include all potentially promising interventions that could be used in primary care without being overly complex and unwieldy. It was appreciated, however, that a broad review could have implications for the literature search in being time consuming and that the synthesis, interpretation and presentation of data gained from heterogeneous studies can be challenging. In the following paragraphs I describe our objectives and discuss the choices we made with regard to formulating our research questions.

Objectives of this review

The *a priori* objectives for this systematic review were:

1. To locate and describe studies evaluating interventions aimed at improving adherence to antihypertensive medication
2. Undertake a critical review of the quality of the methods of these interventions looking in particular at study design and validity
3. Summarise the effectiveness of the above interventions
4. Indicate areas for future research

Types of studies

We decided to consider only randomised controlled and quasi-experimental studies for inclusion in the review. These designs are superior when answering questions about the effectiveness of health care interventions and are more reliable than observational study designs such as case-control or cohort studies, which are more suitable to address questions on, for example, disease aetiology, exposure to risk factors, or incidence of disease.

Types of participants

Our population of interest included adult people diagnosed as having raised blood pressure in a primary care, outpatient or other community setting. We anticipated that this population would be heterogenous and, for example, might include patients who had either newly diagnosed or established hypertension, were controlled or uncontrolled in respect to a pre-defined blood pressure threshold, or non-adherent after an initial adherence enhancing strategy. Given that all these types of patients present in day-to-day general practice, we felt that a narrower focus with regard to the study population would have been inappropriate. However, we appreciated that there may have been important differences in effects among the various subgroups of, for example, people with newly diagnosed or established hypertension, and planned to take this into account in the analysis and interpretation of the results. With regard to the inclusion criteria, we made no restrictions in terms of age, sex, race, educational status, or presence or absence of any comorbid conditions such as angina or diabetes, in order to reflect people usually seen in a typical primary care setting. We excluded participants with secondary hypertension, for example, related to pregnancy or endocrine causes.

Since there is no internationally agreed threshold above which blood pressure can be called 'raised' or 'controlled' (as discussed in section 2.3.1), we decided to include all studies that used the definition of 'high blood pressure' in their inclusion criteria and provide details about individual cut-off points for studies included in the review.

We only considered studies for inclusion that were conducted in a community setting. The only exception was hospital outpatient clinics, if participants were not hospitalised and subsequently followed up in the community.

Types of interventions

We evaluated various kinds of intervention including, but not exclusive to:

1. Education to carers and patients (e.g. counselling, health education)
2. Dosage regimens
3. Involvement of allied health professionals (e.g. nurses, pharmacists)
4. Monitoring (e.g. vial caps, blood pressure self-measurement)
5. Motivation (e.g. financial incentives, reminder packages, reminder aids including diaries or follow-up appointments)

This grouping of interventions laid out in the protocol was arbitrary and partly based on the classifications used in previous systematic reviews. However, we realised that some interventions would potentially not be easy to assign to a particular group due to mixing of different strategies or complex factorial designs (for example, a nurse-led intervention using educational and motivational strategies). We did not impose any restrictions on the timings, frequency or duration of the interventions, which we realised would be variable.

We specified that acceptable control groups should either receive no intervention or 'usual care'. We appreciated that usual care is often not exactly defined and may vary from study to study, but it was thought that this information, if missing, could be sought from the study authors.

Types of outcomes

Our primary outcomes of interest were adherence to blood pressure lowering medication and blood pressure. We did not demand explicit criteria for establishing the presence of those outcomes because adherence and blood pressure have been measured and defined in a variety of different ways. We chose these outcomes to be our primary outcomes because they were likely to be meaningful to people making decisions about how to address the problem of non-adherence in the community. We also planned to collect information on costs if provided by the study authors.

3.4.2 Literature search

Defining the research question in advance was essential for determining the key components to focus on in our initial search strategy. Due to the nature of the various and often complex interventions and outcomes that we expected to find in studies of interventions to improve adherence, we designed our search strategy in close collaboration with Margaret Burke, search co-ordinator from the Cochrane Heart Group. To help construct our search strategy, we went through articles already available to us and listed all search terms that we felt would be relevant for our literature search.

We initially identified original RCTs by an all-language search of articles (any year) in the Cochrane Controlled Trials Register (CCTR), MEDLINE, EMBASE and CINAHL in February 2002, using an approach advocated by the Cochrane Heart Group (see http://www.epi.bris.ac.uk/cochrane/strategy.html for further information). In addition,

we also searched the National Research Register, Current Controlled Trials and PsychInfo.

Figure 8 provides details about the search terms that we used for searching the Cochrane Controlled Trials Register. In addition, we screened the references of all retrieved articles as well as manuscripts that were present in our individual files to identify additional publications. We also contacted study authors of all included studies and experts in the field about other relevant trials or unpublished material.

Figure 8 Search strategy used to identify RCTs of adherence improving interventions in hypertension in the Cochrane Controlled Trials Register [a]

1	HYPERTENS*
2	BLOOD-PRESSURE*:ME
3	(BLOOD:TI near PRESSURE:TI)
4	BLOOD-PRESSURE-DETERMINATION*:ME
5	BLOOD:TI next PRESSURE:TI near MONITOR*:TI
6	#1 or #2 or#3 or #4 or #5
7	PATIENT near COMPLIANCE
8	COMPLIANCE and :TI or ADHERENCE:TI
9	PATIENT next EDUCATION
10	ADHER* or MOTIVAT*
11	AMBULATORY-CARE*:ME
12	AMBULATORY:TI
13	COUNSEL*
14	FEEDBACK
15	REMINDER-SYSTEMS*:ME
16	REMIND*
17	DRUG-INFORMATION-SERVICES*:ME
18	ATTITUDE-TO-HEALTH*:ME
19	EDUCATION* next METHODS
20	EDUCATION* next MATERIAL*
21	PUBLICATIONS*:ME
22	PAMPHLET* or BROCHURE* or LEAFLET* or POSTER*
23	#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22
24	#6 and #23

[a] slightly amended search strategies were used for searching MEDLINE, EMBASE and CINAHL

3.4.3 Study selection

Two of the authors (KS and TF) assessed lists of citations and abstracts produced by the initial database search independently and in duplicate. We were not masked with regard to authors or journal. We selected studies for review if they fulfilled our inclusion criteria as outlined above, using an in/out sheet (Appendix 1). We did not include

studies that tested interventions not designed to increase adherence or where participants suffered from secondary hypertension (for example, due to endocrine causes or pregnancy related). Each reviewer indicated whether a citation was potentially relevant (that is, appearing to meet the inclusion criteria), was clearly not relevant, or gave insufficient information to make a judgment. To be included a study had to meet all of the inclusion criteria. We resolved differences by discussion and obtained reprints of all potentially relevant citations.

3.4.4 Data extraction

We (KS and TF) independently extracted data in duplicate concerning study design, methods, clinicians and patients, interventions, outcomes and potential sources of bias, using a structured data collection form (Appendix 2) designed with Microsoft Word2000® software. The purpose of this data extraction form was to serve as: a) a visual representation of the review question, b) a record of the decisions that occurred during the review process and c) a database from which to conduct the analysis. We designed this data collection form based on details with respect to our final research question and piloted it on five studies, which led to a number of minor amendments. We kept both electronic as well as paper copies of completed data extraction sheets, as identifying and addressing errors was easier on paper forms. After we had extracted data from all included studies, we compared data extraction forms completed by two reviewers to identify and address errors. A third rater (SE) verified the data extraction and made corrections where necessary. Any disagreement was resolved by consensus. We wrote to 28 corresponding authors of studies to request missing data and clarify study details if required.

3.4.5 Data management

We prepared the Cochrane version of this systematic review using ReviewManager® version 4.1 (Update Software, Oxford, 2003). This software is essential for every Cochrane Review and assists with data management, quantitative analyses and generation of the review and is supplied free of charge to every Cochrane Reviewer.

3.4.6 Quality assessment

Two reviewers assessed the quality of the studies independently and in duplicate. We handled disagreements by consensus and requested additional information about study

design from the authors if necessary. We extracted data on potential sources of bias including the method of patient randomisation, blinding of the outcome assessor, and differential losses to follow-up rather than providing a summary score. The approach we adopted is that advocated by the Cochrane Heart Group.

3.4.7 Quantitative data analysis

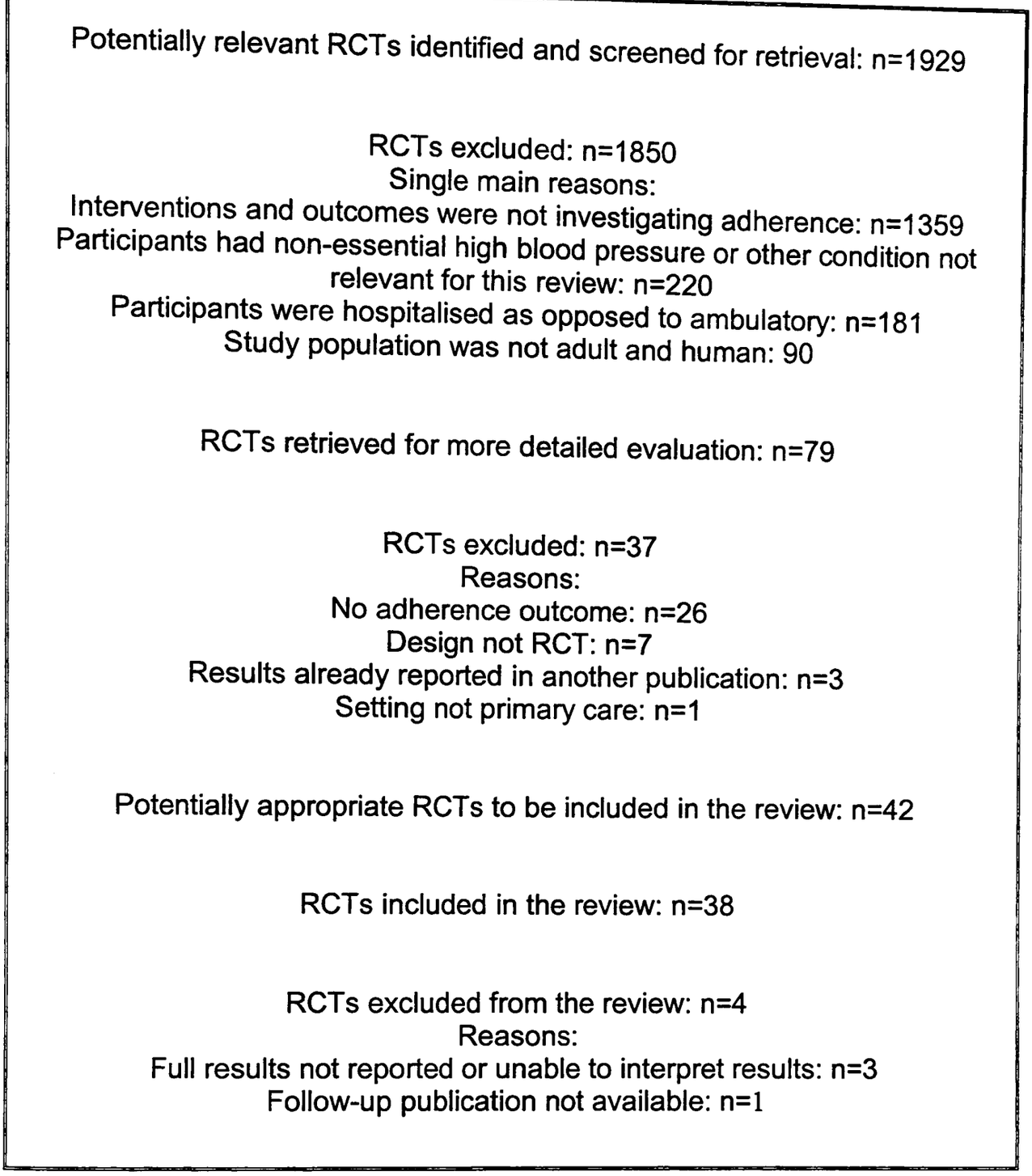
Due to heterogeneity between studies in terms of interventions and the various methods that were used to measure adherence, we felt that pooling of the results was inappropriate. We grouped and reported the individual arms of factorial trials separately in the respective groups.

3.5 Results

3.5.1 Study characteristics

We screened 1929 citations and included 38 studies that met all the predefined criteria, involving a total of 15519 patients and testing 57 different interventions (Figure 9).[10,180-216] Appendix 3 summarises the characteristics of included RCTs, which were conducted between 1975 and 2000. The majority of trials were performed in the USA (n=20) and Canada (n=8) with the remainder located in Europe (n=8), Australia (n=1) and South Africa (n=1). Study participants fell into a number of different categories that included newly diagnosed patients, patients with established hypertension on medication, patients with controlled or uncontrolled hypertension, patients adherent or non-adherent to medication or infrequent attendees at clinic. Given the lack of a generally accepted categorisation, we grouped studies into the following four pragmatic categories: (i) simplification of dosing regimens, (ii) patient education, (iii) patient motivation, support and reminders and (iv) complex health and organisational interventions including interventions in combination. Adherence was measured in different ways, including self-report, direct questioning, pill counts, and the medication event monitoring system (MEMS®), and various criteria for adherence were used in the different studies. We treated the different arms of studies using a factorial design as separate studies and present the results of these accordingly. All studies examined both men and women in varying proportions, and the duration of follow-up ranged from two to 60 months.

Figure 9 Trial flow for systematic review



3.5.2 Quality of the primary studies

The methodological quality of included studies was generally low (Appendix 4). The randomisation process was reported and provided adequate concealment of allocation in only 10 out of the 38 studies (26%).[182,185,187,188,193,204,205,207,214,216] The outcome assessors were blind to treatment allocation in 12 studies (32%).[10,185,188,190,193,198,202,205-207,212,214] Losses to follow-up were well documented in 33 studies (87%). Only eight trials (21%) reported a power calculation,[187,191,198,200,205,207,210,212] and most of the remaining trials

appeared too small to detect clinically important differences. None of the included studies fulfilled all the quality criteria.

3.5.3 Effect on adherence and blood pressure

Individual RCTs reported results on adherence in many different ways, making a pooled analysis inappropriate (Appendix 3). Nineteen studies reported an improvement in adherence alone, seven found improvement in adherence combined with a reduction in blood pressure, and in seven studies a reduction in blood pressure occurred without an increase in adherence. Fifteen of the included studies (40%) did not report a blood pressure outcome, and none of the studies examined major clinical endpoints. Please note that in the following section the total number of RCTs (that is, interventions) is 58 rather than 38, because some factorial RCTs tested interventions in different categories, which therefore counted more than once.

Simplification of dosing regimens

In this group, nine RCTs tested nine different interventions. Simplifying dosing regimens improved adherence in seven out of those nine studies,[182,184,186-190] with relative improvement in adherence in terms of numbers of participants who took 80% or more of their medication between 8% to 19.6%. All the studies that used objective outcome measurement (MEMS®) showed an improvement in adherence through the use of once-daily instead of twice-daily dosage regimens,[182,186,188-190] although four of these compared two different drugs.[182,186,188,189] Only one study showed an increase in adherence (90% vs. 82%, $p<0.01$) together with a reduction in systolic blood pressure of 6mmHg systolic ($p<0.01$).[188]

Patient education

Six RCTs tested six different interventions in this group. Patient education seemed largely unsuccessful. Only a single small trial improved adherence (93% vs. 69%, $p<0.002$) with no reported effect on blood pressure.[195] This study used group education in groups of 15 people over 90 minutes and additional postal information leaflets at one, three and five months.

Patient motivation, support and reminders

Sixteen RCTs tested 24 different interventions in this group. Motivational strategies were partly successful in 10 out of 24 study interventions with mostly small increases in adherence up to a maximum of 23%.[192,197,199,202,208,209,214] All of these studies used less reliable methods of measuring adherence such as pill counts, self-report, direct questioning, and prescription refill records. Successful interventions included daily drug reminder charts (mean adherence score 82.4% vs. 70.4%, p=0.002),[197] training on self-determination (4.6 out of 7 weeks adherent vs. 3.3 weeks in the control group, p<0.001),[199] reminders and packaging (alone and in combination, increase in adherence between 8% for reminders alone and 23% for reminders and packaging in combination, p<0.05),[214] social support (98% achieved maximum adherence score vs. 93%, p<0.05),[192] nurse phone calls (96% achieved maximum adherence score vs. 91%, p<0.05),[192] family member support (53% high adherers vs. 40%, p<0.05),[209] electronic medication aid cap (mean adherence 95% vs. 78%, p=0.0002),[208] and telephone-linked computer counseling (18% adherent vs. 12%, p=0.03).[202]

Complex health and organisational interventions including interventions in combination

Seventeen RCTs investigated 18 different interventions in this group. Eight complex interventions successfully increased adherence, ranging from 5% to a maximum of 41%.[180,201,206,213,215] Worksite care through specially trained nurses providing patient-tailored care improved adherence (67% vs. 49%, p<0.005) and led to a net reduction in blood pressure of 4 mmHg between intervention and control groups (p<0.001).[206] A combination of home visits, education and special dosing devices improved adherence in a small trial of 16 patients (92% vs. 71%, p<0.001).[201] A strategy involving an educational leaflet, a telephone reminder, a mailed reminder and an educational newsletter was successful in both previously treated hypertensive patients ('medication possession ratio' 82% vs. 48%, p<0.05) and those who were newly diagnosed (93% vs. 52%, p<0.05).[213] Two fairly recent trials reported weak evidence of an effect of a patient-centred pharmaceutical care model (compliance score 0.23 vs. 0.61, p<0.05)[215] and a combination of structured brief questioning protocol with advice, information and referral to the family practitioner (62% adherent vs. 50%, p<0.05).[180] In this study blood pressure was also better controlled in the intervention group (35.7% became controlled vs. 17.1%, p<0.05).

3.6 Discussion

3.6.1 Key findings

From this systematic review, simplification of dosing regimens increased adherence in seven out of nine studies, with improvement in adherence ranging from 8% to 19.6%. Adherence in these studies was mainly measured with electronic monitors, and these results confirm findings from past research. In a small number of studies, nurse led interventions, which were often complex, were also effective in increasing adherence. There was mixed evidence for the effect of motivational and more complex interventions. Education alone appeared largely unsuccessful. A combined effect on adherence and blood pressure was only observed in 7 out of 58 study interventions (12%).

3.6.2 Interpretation of the results in the light of previous research

This review differs from previously published reviews in that we used a more comprehensive search strategy and different methodology. Compared to the latest reviews on adherence enhancing strategies,[12,178] we found and included considerably more studies (nine and 32 more studies respectively). The review by Morrison extracted categorical data in preference to continuous data, and ignored evidence from trials where data could not be converted. This may have been particularly relevant for the results in the group with changes in medication dosing, where we come to the opposite conclusion. This review is also different in that we have reported the results from individual arms of factorial trials separately.

We agree with the review by McDonald and colleagues that for complex interventions it is often difficult to estimate the independent effects of individual interventions.[12] It also remains difficult to disentangle specific adherence effects as opposed to non-specific effects of increased attention. Our findings confirm that even the most effective interventions do not appear to lead to large improvements in adherence and treatment outcomes.

An earlier review of research on adherence reported benefits of educational interventions in improving adherence.[177] However, we were unable to confirm this finding, perhaps because we only included RCTs in our review.

3.6.3 Limitations of this review

Comparing the RCTs included in this review was difficult. Many RCTs showed marked heterogeneity in terms of participants, interventions and outcomes. Study authors also measured and reported adherence inconsistently. Individual RCTs demonstrated variable and often poor methodological quality, particularly with regard to randomization, blinding of outcome assessment and losses to follow-up, whilst the sample sizes of many trials were too small to detect clinically relevant differences. Rather surprisingly, 15 out of the included 38 studies (40%) did not report a blood pressure outcome, and none reported major clinical endpoints.

There are also some difficulties in interpreting the results of this systematic review. Adherence was measured (for example, self-report, pill counts, direct questioning, electronic monitoring, drug blood levels) and calculated in different ways (for example, using arbitrary cut-off points to define adherence, such as 80%), and in addition was usually assessed unblinded to allocation status, which made the comparison of RCTs difficult. Levels of adherence in the control groups of the trials studied ranged from 12% to 94%, which is indicative of the heterogeneity in both the criteria for defining adherence and the participants studied.

With no agreed definitions on how adherence should be measured and defined, it is not surprising that for most interventions the impact on adherence and blood pressure appears to be variable. Given the different definitions for adherence that have been adopted in individual RCTs, it has not been possible to examine the relationship between adherence to medication and subsequent blood pressure control. Our categorisation and grouping of trials was developed specifically for the review, and the group allocation of some trials might be debatable.

3.6.4 Implications for practice

Our findings suggest that introducing simpler dosing regimens could be effective in improving adherence, but the effect on subsequent blood pressure reduction has not been established and may not be clinically important. The results of various motivational and more complex interventions are promising, although there is insufficient evidence to suggest a single approach. In many countries, the role of allied health professionals such as nurses or physician assistants is expanding, which may lead to new management opportunities for tackling adherence-related problems in patients

with high blood pressure. However, we suggest that innovative approaches should be introduced in the context of further RCTs. It is important that physicians are aware of the various reasons for poor adherence and aim to simplify dosing regimes as far as possible.

3.6.5 Implications for future research

The results of this review highlight a number of problem areas in adherence related research. Many studies used unreliable methods of measuring adherence such as self-report and pill counts. It appears that electronic monitoring provides more objective and reliable results and, in addition, produces data on medication taking patterns. Although a large number of studies have been conducted in this area, larger trials of higher quality are needed that use reliable methods of measuring adherence and that also investigate the relationship between adherence and blood pressure reduction. This is particularly important in the context of an increasing elderly population of people who often take multiple medications. Hypertensive patients may fail to take their medication due to the long duration of therapy, the symptomless nature of the condition, side effects of medication, complicated drug regimens, lack of understanding about hypertension management, lack of motivation and the challenge to individual patients' health beliefs.[41,131] It would seem logical that future studies should try and adopt a 'tailored' approach aimed at individual patients and addressing the above-mentioned barriers to adherence. Using combinations of strategies that include simpler dosage regimens, patient motivation and that involve other health professionals in a patient-centered approach should be further investigated. In addition, patients' views should be taken into account when piloting interventions, and the interventions themselves should be based on shared decision-making and a true partnership between patient and practitioner.[145,217-219] Finally, it is of paramount importance that every study which evaluates an intervention to increase adherence to blood pressure lowering medication should also measure blood pressure as a secondary outcome, which will help establish the often unclear relationship between adherence and blood pressure control.

3.6.6 Implications for this thesis

This systematic review highlighted a number of issues that were relevant for the design of the randomised trial, which I describe later in this thesis (Chapter 5). In particular, the design of the intervention and the measurement of adherence emerged as topics

requiring careful consideration. The main impact of this review on the trial design was that a) electronic monitoring replaced our initial choice of outcome assessment, namely self-report of adherence and analysis of repeat prescriptions, and b) that the intervention had to take into account patients' individual needs rather than providing a 'blanket approach' like, for example, the provision of group-based information or education.

3.6.7 Conclusions

Simplification of dosing regimens appears to be the most promising intervention to increase adherence to blood pressure lowering medication. In terms of other strategies, we cannot recommend a single approach, and a combination of interventions appears most promising. We believe these should include the simplification of dosage regimens and involve other health professionals such as nurses who provide tailored care to individual patients. The evidence for the effect of motivational and more complex interventions is mixed and inconclusive. The results of this review should be interpreted with caution due to the poor methodological quality and heterogeneity of many trials included in this review. The findings emphasize the need for further RCTs with sufficient power and of rigorous methodology.

The increasing role that nurses play in the management of hypertension in the UK and some existing evidence from this review that nurse led interventions may be effective prompted us to develop and evaluate a pragmatic nurse led intervention, which we evaluated by means of an RCT (see Chapter 5).

3.7 Summary

This chapter described a systematic review of RCTs evaluating interventions to improve adherence to blood pressure lowering medication and concludes the literature review for this thesis. In the following chapter I will outline how the findings from this systematic review and Chapter 2 have informed the discussion of the choice of methods that I have used for the studies described in Chapters 5 to 8.

4 Overview of methodological issues

4.1 Introduction

This chapter explains how the literature reviews informed further clarification of, and changes in, the research question of the studies described in this thesis, particularly with regard to the design and methods of the RCT reported in chapters 5 and 6. The findings from both the traditional literature review (Chapter 2) and the systematic review of RCTs of interventions to increase adherence to blood pressure lowering medication (Chapter 3) led to significant changes in the research question. In the following sections I summarise the most important findings from both literature reviews that are relevant to this thesis and discuss the issues arising from those findings.

4.2 Summary of important research themes

The literature reviews revealed a number of themes, of which many have to a greater or lesser extent influenced the framing of the research questions. With regard to developing an intervention to increase adherence in primary care, two themes emerged which appeared to be of particular importance: first, involving patients in their management and second, a multi-professional approach to managing chronic disease. Other important areas that became apparent are the definition and measurement of adherence and the various reasons for non-adherence to medication.

4.2.1 Patient-centredness and shared decision-making

Traditionally the relationship between health care professionals and patients was often based on a paternalistic model, which did not take into account patients' values and preferences with regard to making decisions about whether or not to accept treatment decisions. In the past few years a growing body of evidence has emerged which highlights the importance of involving patients, particularly in the management of their chronic diseases.[141,142,148] What do we really mean by 'involving patients' or 'patient centredness', though, and how can we address these issues in health care interventions? This question, unfortunately, is difficult to answer, as there appears to be considerable uncertainty about what these expressions mean.[142,144] A helpful construct appears to be the idea of improving communication, about information that patients need and want to know (for example, with respect to diagnosis, management, risks and prognosis of their condition), about sharing decisions as well as responsibility, and about becoming true

partners when making decisions about health care.[71,149,151-153] So far, there is little evidence that this is happening during the consultation.[153] Tools which might help to improve communication and patient involvement include more time during the consultation,[151] improving the language used when talking about risks,[156,157] or the use of decision aids.[159]

4.2.2 Multi-disciplinary approach

A multi-disciplinary approach is widely advocated to provide care for people with chronic illnesses.[59,60] Although there is evidence that practice nurses can offer an effective service, there is little evidence from a recent review by Oakeshott and colleagues that nurse-led management of hypertension is effective in terms of improving blood pressure control in primary care.[65] The authors concluded that the most important differences between GP and nurse-led care would be improved antihypertensive prescribing and adherence to treatment due to rigorous application of national guidelines. For example, the use of risk charts in coronary heart disease by trained practice nurses and GPs in UK primary care led to a reduction in systolic blood pressure, mainly due to increased prescribing.[220] Further RCTs in this area are needed to evaluate whether nurse-led care can lead to improved blood pressure control.[65]

A small number of RCTs evaluated the effect of nurse-led care on adherence to blood pressure lowering medication.[192,206,207,221] These trials were heterogeneous with regard to study populations, interventions and outcomes, but showed some promising results in terms of improving medication adherence (see Chapter 3 and Appendix 3). The World Health Organization now encourages a multi-disciplinary approach to improve medication adherence not only in hypertension, but also in a number of other clinical conditions.[2]

4.2.3 Outcome measurement and definition of adherence

The literature reviews described earlier in this thesis (Chapters 2 and 3) have shown that adherence is defined and measured in many different ways, making a comparison of individual studies difficult. Although no 'gold standard' of measuring adherence exists, electronic devices appear to be the most accurate instruments in assessing patient adherence. Their advantage lies in the precision of data in terms of logging the exact time and date of each opening, but their main drawback so far has been the relatively high cost. Electronic medication monitors have therefore mainly been used in research rather than in day-to-day clinical practice.

4.2.4 Reasons for non-adherence

There are a number of reasons why patients can find it difficult to take their medicines as prescribed. As outlined in Section 2.4.7, these may be related to: (a) the drugs in terms of side effects, number of tablets, or duration of treatment, (b) the health professional with regard to poor communication, lack of information or suboptimal follow-up, or (c) the patient with respect to forgetfulness, mistakes, beliefs about medication, or external factors. However, reasons for non-adherence are usually complex and multifactorial and not due to a single cause.[2]

4.2.5 Inadequacies within the existing literature

The review of the literature has identified a number of inadequacies in adherence research. There is a continuing debate with regard to defining and measuring adherence. Since these issues are not clear-cut, it is hardly surprising that the latest scientific review of interventions to enhance patient adherence to medication prescriptions concludes that the literature in this field "remains surprisingly weak" and that "there are only a few rigorous trials of adherence interventions".[12]

A number of major issues still remain largely unanswered. How should we define adherence? How should we measure adherence? What is the true level of adherence in the community? What interventions work to improve adherence? How does adherence relate to clinical outcomes? What do patients think about adherence?

Studies that have evaluated interventions to improve adherence to blood pressure lowering medication defined adherence in many different ways, making a comparison of studies difficult. In addition, adherence has been measured using a variety of methods, with only a minority of studies using comparatively reliable outcome measures such as electronic medication monitoring. The often quoted estimate that only about 40-50% of people are adherent to medication also seems to be based on little reliable data. Evidence from recent randomised trials suggests that although simpler dosing regimens increase adherence, this does not necessarily lead to better blood pressure control.

4.3 Implications of the literature review for the design of the study

The main themes identified in the literature review highlighted a number of general implications for the design of the studies described in this thesis.

First, it is important that studies use the most reliable outcome measures available. This should, where possible, include electronic monitoring, which can provide data on dose timings and patterns of medication taking. Such data are unobtainable by any other method. Although electronic monitors are still relatively expensive, the modest increase in research budgets is often more than outweighed by the quality and richness of the data obtained.

Second, to be able to improve adherence, a more standardised approach to defining desired levels of adherence and how to measure it is needed. The commonly used cut-off point of '80% adherence' above which adherence is thought to be sufficient is in many cases meaningless and not based on pharmaco-epidemiological evidence linking frequency of medication taking with clinical outcomes. Indeed, it may be preferable to avoid artificial cut-off points altogether and utilise a continuous measure of adherence in the analysis of adherence data.

Third, investigations aiming to improve adherence should be multi-disciplinary and involve patients in the management of their condition. An important aspect for the design of adherence improving interventions is to allow a tailored approach to identifying and solving medication problems in individual patients.

Fourth, there has thus far been little research on the relationship between adherence and subsequent 'control' of the disease. We do not really know what level of adherence is necessary for individual drug classes used in a number of medical conditions, as some drugs are much more 'forgiving' than others in terms of missed doses and the timing of ingestion. Although so far even the most effective interventions have had only modest effects, these could be effective on a population level in reducing the overall burden of disease.

4.3.1 Impact of the literature review on the research question and design

The original aim of this thesis was to investigate new ways to improve adherence to medication in chronic disease, using hypertension as the target condition. The research described in this thesis aimed to address health care and patient related factors while acknowledging the fact that it is the patient's agenda that determines whether patients choose to take their medicines or not.

The main objective was to evaluate an intervention to increase adherence to blood pressure lowering medication by means of a RCT. The findings of the literature review

led to the development of an intervention that aimed to encompass most of the areas that were identified as important: (a) a nurse-led approach, (b) an emphasis on patient involvement, (c) flexible strategies adapted for individual patients, and (d) objective outcome measurement of adherence.

It seemed logical that any intervention to increase adherence to medication would need to be easy to introduce into routine care. We therefore combined components of the interventions that showed promising results in previous RCTs into an intervention that could be delivered by practice nurses without the need for extensive training.

4.4 Choice of methods

4.4.1 Overview of desirable research methods

A number of publications have acknowledged the lack of a sound evidence base to inform many of the clinical decisions that are made in day-to-day general practice.[3,222,223] One of the reasons for the lack of evidence for many interventions used in primary care is that randomised trials have traditionally played a less dominant role in primary care research compared to observational studies.[224] It is generally accepted that randomised controlled trials are the method of choice when evaluating the effectiveness of health care interventions. The main study described in this thesis is therefore a randomised trial, and the following sections describe in more detail the justification for using this design for the main study. In addition, I will outline the reasons for using observational study designs for the other studies described in this thesis.

4.4.2 Choice of a randomised controlled trial as the design for the main study

Since one of the main aims of the research described in this thesis was to evaluate the effectiveness of an intervention to increase adherence to blood pressure lowering medication, the randomised trial was the obvious choice for the conduct of the main study. This trial was informed by a systematic review of RCT as described in Chapter 3. There is general consensus that the randomised controlled trial represents the current 'gold standard' in study design when evaluating the effectiveness of health care interventions, mainly because the process of patient randomisation allows controlling for known and unknown confounding factors. Various trial designs can be used in

primary care, which may include patient preference trials, RCTs in single patients (so-called n-of-1 trials), factorial trials, crossover trials, or cluster randomised trials.[3] The trial described in Chapters 5 and 7 is a parallel group pragmatic trial with randomisation by individual.

4.4.3 Choice of outcome measures

Ideal outcomes for this trial would have been direct clinical endpoints such as mortality or morbidity in terms of heart attacks and strokes. Estimation of these endpoints would have required a larger sample size and a much longer study duration, both of which were outside the scope of this study. Instead, adherence and blood pressure were chosen as surrogate endpoints, which aim to predict the direct measures of harm, that is, heart attacks and strokes. Although blood pressure is not in itself a direct measure of either harm or clinical benefit, it is widely accepted as a risk factor for heart attacks and strokes.[5,6,37,225] Although the relationship between adherence and blood pressure control has not been universally proven, adequate adherence is regarded as an important prerequisite for improving the outcomes in chronic disease.[2] Both therefore fulfil the criteria for surrogate endpoints and are also relatively easy to measure.

The initial methods of choice for measuring adherence were patient self-report and prescription refill records. However, based on findings from the literature review and discussions with experts in the field at a workshop on methods in adherence research in Pittsburgh, it was decided to use electronic medication monitors for outcome measurement of adherence instead. These, as outlined before, provide much more reliable data on medication taking than the initial methods of choice. Chapter 5 provides more detail about the way adherence was measured and defined in this study.

4.4.4 Rejected research methods

The initial design of the RCT was a 2x2 factorial trial, which would have allowed simultaneous evaluation of a second intervention, that is, an information leaflet on problems with medication adherence. During the planning phase of the study new evidence emerged from a trial conducted in Bristol, which raised the possibility of an interaction between nurse-led adherence support and providing an information leaflet.[226] When conducting factorial trials it is usually assumed that there is no interaction between the interventions tested in the trial arm. If an interaction is expected, then the trial size has to be inflated considerably to provide enough power to detect or rule out

this interaction. In the light of the evidence[226] that there was a realistic chance of such an interaction for the proposed trial, we abandoned our original idea and changed the trial to a parallel group design. We felt that the information leaflet was the least important component of the intervention and, to make the intervention less complex, did not include the leaflet in our parallel group design.

4.5 Ethical implications

Having reviewed the literature in the field of adherence and designed the study protocol, I reassessed the study design by taking into account principles of biomedical ethics.[227] One of the most popular ways of thinking in the field of biomedical ethics is the idea of 'principlism', which was first described by the American philosophers Beauchamp and Childress in the 1960s.[228] The concept of principlism argues that by taking into account the four principles of autonomy, non-maleficence, beneficence, and justice, any medico-ethical dilemma can be analysed, which also applies to research projects.

Based on these principles, there are three types of ethical problems that arise in healthcare research, which include (a) goal-based questions, that is the outcome and moral worth of the study, (b) duty-based questions relating to the risks and handling of research participants, and (c) rights-based questions in connection with informed consent and confidentiality.

Ethical justification for conducting the trial

The trial was designed to evaluate the effect of a nurse-led intervention on adherence to blood pressure lowering medication. As outlined above, the design of this study took into account findings from past research, which have been searched for and evaluated in a systematic way. Both the protocols for the systematic review and the randomised trial underwent peer review by the Cochrane Collaboration and the Medical Research Council, which funded the main trial. There is ample evidence in the literature that further research in this area is needed and relevant to the provision of healthcare.[2]

Duty to research participants

As already discussed, involving patients in their management was an important aspect of this study, thereby increasing their autonomy in terms of getting more involved in the management of their condition. There did not appear to be any major risks for patients as a result of this intervention that would not also occur as part of routine medical care.

Any additional risks (for example, an increase of drug adverse effects due to previously non-adherent patients starting to take their medicines more regularly as a result of the intervention) appeared acceptable under the circumstances.

Consent and confidentiality

To protect the rights and respect of individuals, we designed an extensive patient information sheet to allow study participants to give informed consent to take part in the study. Informed consent was sought in a non-coercive way, and patients were reminded on several occasions that taking part in the study would be voluntary, and that not taking part in the study would not in any way affect their routine care. At all times patient confidentiality was respected according to the Data Protection Act 1998.

Ethics committee approval

This study was designed and conducted in accordance with the *MRC Guidelines for Good Clinical Practice in Clinical Trial*, and approval from the South and West Multi-centre Ethics Committee was granted.[229]

4.6 Summary

This Chapter summarised how the findings from the literature review influenced the aims and objectives of the main study in this thesis and the methods used in the trial. It drew attention to some of the theoretical foundations for the study, which led to a reflection on the overall research design. In the next chapter I describe the methods used in the RCT in more detail to provide information that allows assessing the internal and external validity of the study.

5 Methods of the RCT of nurse-led adherence support in hypertension

5.1 Introduction

This chapter describes the methods used in the RCT of nurse-led adherence support in hypertension described in Chapter 6. The project was part of a MRC Training Fellowship in Health Services Research and funded by the Medical Research Council and the Division of Primary Health Care. This chapter is reported according to the revised recommendations for improving the quality or reports of parallel group randomised trials (CONSORT statement) and includes further additional information that is relevant to this thesis.[230]

Tom Fahey and Tim Peters originally conceived the study, which was designed by the three of us. Tim Peters conducted the randomisation, and I was the principal investigator on this trial, which included responsibility for the day-to-day running of the study and management of the trial budget.

5.2 Objectives

The main objective of this study was to evaluate the effectiveness of a nurse-led adherence support intervention aiming to increase adherence to medication and reduce blood pressure in uncontrolled hypertensive people. The primary outcome was adherence, defined as 'timing compliance'. Secondary outcomes were systolic and diastolic blood pressure, 'taking compliance' and 'correct dosing'.

5.3 Study design

As outlined in Chapter 4, this trial was designed as a pragmatic, primary care based parallel group trial with randomisation by individual, comparing nurse-led adherence support in addition to usual care with usual care alone.

5.3.1 Justification of choice of study design

This trial aimed to improve health care to uncontrolled hypertensive patients and provide a basis for decisions about the delivery of care for this patient group. Results of efficacy trials of antihypertensive drugs have shown that treating high blood pressure

can lead to a reduction of heart attacks and strokes.[5,37] Since various components that were combined in the intervention have shown promising results in RCTs (see Chapter 3), a pragmatic randomised trial was conducted to help decision makers and clinicians in primary care assess the potential value of the intervention in the routine clinical setting in a representative group of patients.

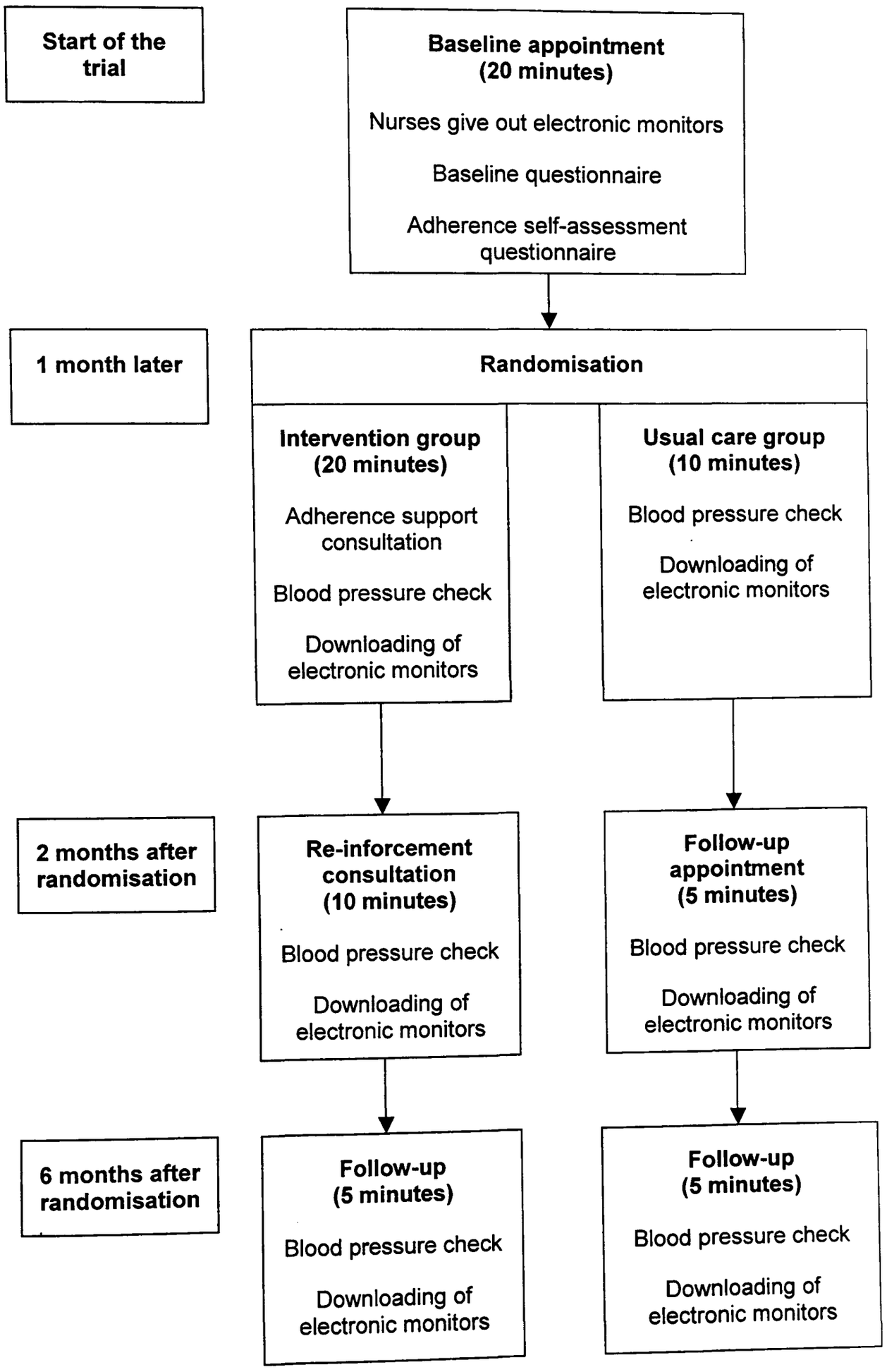
5.3.2 Adjustments made to the study methods

In addition to modifications to the study design described in the previous chapter, the main change to the study protocol affected the outcome measurement of adherence. The initial strategy for measuring adherence was to use a mixture of patient self-report and repeat prescribing data. Since electronic monitoring has emerged to be a superior method in terms of accuracy and validity, I adapted the study protocol to incorporate the use of electronic monitors instead of using repeat prescribing data.

5.4 Overview of the study schedule

Figure 10 gives an overview of the study schedule. Consenting participants attended an initial appointment in which they were given an electronic medication monitor and informed about the trial schedule. In the intervention group, the main adherence-support consultation took place after a baseline-monitoring phase of 30 days, followed by a reinforcement appointment two months later. All study participants were followed up for six months.

Figure 10 Overview of study appointment schedule



5.5 Setting and practice recruitment

I wrote to 82 general practices in Avon, UK. Of the 45 practices that replied, 24 gave time constraints and staff shortages as the main reasons for declining to take part. Twenty-one general practices in rural and urban settings took part in the study. Fourteen practices were teaching practices, and 11 belonged to a Culyer-funded research consortium. All practices ran nurse-led clinics, which contributed to the care of their hypertensive patients.

5.6 Participant recruitment and eligibility criteria

The overall aim of the recruitment strategy was to ensure to be as inclusive as possible in order to give all patients registered with the practice who fulfilled the inclusion criteria the same chance of being in the trial. Participating practices performed a computerised search of their practice registers for patients who were coded as having hypertension, were prescribed antihypertensive medication and had a latest blood pressure recording of ≥150 mmHg systolic and/or 90 mmHg diastolic (British Hypertension Society (BHS) audit standard for general practice).[19] We recruited eligible participants from June 2001 to December 2001 and followed them up until December 2002.

Due to the pragmatic nature of the trial we aimed to keep the exclusion criteria to a minimum. GPs and practice nurses screened this list and excluded patients in whom the following reasons for exclusion were present: (1) individuals did not control their medication intake (e.g. some nursing home patients), (2) secondary hypertension (e.g. endocrine, renal or pregnancy related), (3) severe dementia, (4) using a dose organiser, or (5) other reasons given by the practice nurses or GPs for not approaching their patients (for example, terminal illness or recent bereavement). Using computer-generated random numbers supplied by the research team, the practices identified a random sample of patients on this list, stratified by age (<60 and ≥60 years) and sex. The aim of the stratification was to increase the generalisibility of the study by selecting study participants with a similar age/sex distribution as shown for hypertensive adults in the community.[9] The practice nurses or GPs sent information about the study to the sampled patients, asking them to take part in this study.

5.7 Consent

Patients who were potentially interested to take part were asked to return a reply slip to us and subsequently received more detailed information about the study together with a consent form. Study participants were informed that at any stage of the trial they were free to leave the study without giving any reasons and without any consequences to their usual medical care.

5.8 Initial appointment

At the initial appointment, study participants received an electronic medication monitor to be used to assess adherence to one of their blood pressure lowering drugs. The drug to be used with the monitor was chosen by the practice nurse according to a flow chart (Appendix 6). This favoured diuretics to beta blockers and other drugs, since diuretics are commonly used as a first line treatment in hypertension. Guidance on prescribing for hypertension has been issued by the Bristol South & West Primary Care Trust and the United Bristol Healthcare Trust in 2002 and has been made available to all general practices in Bristol, recommending the use of bendrofluazide and atenolol as first-choice agents for the treatment of high blood pressure.[231] Once-daily preparations were the preferred choice of drugs to be used in the monitors because this dosing frequency is the most common in the drug treatment of high blood pressure. Ideally, we would have used more than one electronic monitor if participants were taking more than one blood pressure lowering drug, but for cost reasons this was not feasible. Study participants were asked to transfer the chosen drug into the electronic monitor themselves.

5.9 Interventions

5.9.1 Theoretical background

We developed this pragmatic intervention using primarily the self-regulatory model of illness behaviour developed by Leventhal, which has been described in more detail earlier in this thesis (Section 2.4.9).[128,130] The particular strength of this model is that it takes into account the individual symptom perception, emotional responses to a health threat and coping strategies such as avoidance. The main aim behind the theoretical development of the intervention was to help patients understand their diagnosis of high blood pressure and why treating their high blood pressure can improve their health outcomes, while simultaneously taking into account individual perspectives of their

illness and its treatment.[232] Thus the development of the intervention was largely guided by the theoretical frameworks and trial evidence outlined in the previous chapters.

5.9.2 Design of the intervention

The intervention that was developed for this trial can be classified as a 'complex' intervention, that is, an intervention that consists of interconnecting and different parts.[233] Complex interventions can be difficult to define and reproduce. They pose, therefore, many challenges if they are to be tested in randomised trials.[233,234] Campbell and colleagues described a framework for the design and evaluation of complex interventions to improve health and advocated a phased approach.[233]

The development of this trial was to a certain extent based on this framework and included sequential phases. The first phase consisted of the review of the literature (see Chapters 2 and 3), which examined the relevant background theory to identify the best choice of the intervention and to predict important confounders and design problems. We aimed to identify the components of the intervention and mechanisms through which they may influence the outcomes by evaluating the qualitative literature in this field. For practical and economical reasons we were unable to conduct an exploratory trial. However, we refined the intervention in consultation with patients, practice nurses, general practitioners and experts in the field and tried to standardise the intervention as much as possible to make this study reproducible.

Key elements of the intervention

Four key features of Leventhal's self-regulatory model were used to develop the main elements of the intervention, which we summarised in a consultation prompt sheet (Appendix 5) for the nurses who delivered the intervention. First, patients' responses to health threats are often guided by illness representations. Part of the intervention was therefore to ask patients about their perceived health risks from high blood pressure and discuss misconceptions. Second, Leventhal describes two parallel and partially independent motivational processes: one that is focused on the problem and one that is focused on emotions. We encouraged nurses to ask patients how they feel about their medication and what they felt their problems were. Third, patients' mental constructs often have both abstract-conceptual and concrete-perceptual content, which the nurses addressed by establishing patients' health beliefs and what they perceived to be their biggest problem with regard to medication taking. Finally, "if-then" cognitive rules often link representations, behaviours and appraisal of outcomes. We therefore

encouraged nurses to design individual solutions to medication problems presented by study participants, taking into account the key features of Leventhal's model.

5.9.3 Delivery of the adherence-support intervention

Since many problems around medication taking result from poor communication between health professionals and patient, the overall objective of the intervention was to find a way to help improving the communication between practice nurses and patients. The key tasks for the participating practice nurses were therefore to elicit the patients' main problems, the patients' perception of these and the social impact of these problems on patients and their families.[235] Relationships between health professionals and patients can take different forms. Three models commonly referred to in treatment decision-making are the paternalistic, the shared, and the informed model.[236] For implementing the intervention we encouraged the practice nurses to follow the shared model by sharing all stages of the decision-making process simultaneously.[151,237]

Practice nurses invited participating individuals to attend an adherence support session lasting a maximum of 20 minutes, followed by a shorter reinforcement session (10 minutes) two months later. The aim of the intervention was to provide an opportunity for patients to talk about any problems with their blood pressure lowering medication in a safe and non-threatening atmosphere and was led by the patients themselves.[13,79,167] During the consultation, practice nurses investigated whether patients understood their diagnosis and agreed with the treatment process. We encouraged the practice nurses to address patient concerns with their medication and to agree tailored strategies to resolve any medication problems.[13,238] To increase consistency, the practice nurses were asked to record the content of the consultation on a one-page prompt sheet (Appendix 5) This prompt sheet contained suggestions for potential issues to be raised, including the most common barriers to adherence.

We designed this intervention in such a way that it could easily be introduced into routine practice. The only adherence-related training provided for the practice nurses was an explanation of the prompt sheet. We encouraged the nurses to find individual solutions to patients' problems taking into account their experience and knowledge of their patients.

5.9.4 Care in the control group

The control group received standard care delivered at their respective practices, apart from blood pressure checks at similar intervals as the participants in the intervention group. Wherever possible, these checks were carried out by another practice nurse who was not involved in delivering the intervention. Given the potential for contamination, all practice nurses were made aware of this risk and strongly and repeatedly encouraged not to change their 'usual practice' for the control patients. Blood pressure was measured according to the guidelines laid out in Figure 1.

5.10 Sample size

We designed this trial to detect a difference in adherence between the two intervention groups receiving adherence support and usual care. We estimated from the existing literature that about 50-60% of patients would be adherent to medication in the absence of the intervention.[10,41] For a target difference in adherence of 15 percentage points (for example 75% in the intervention group and 60% in the control group), a 2-sided 5% significance level and 80% power, we required a total sample size of about 330 participants. However, it is worth remembering that considerable uncertainty exists about the levels and variability of adherence outcomes, resulting in additional uncertainty for the sample size calculation, and that this sample size calculation might imply an unrealistic degree of precision. So far, there is little high quality evidence on the relationship between adherence and blood pressure. However, we felt that from a clinical point of view an increase in adherence of 15% would be important, although we appreciated that this would largely depend on the particular drug in question.

With respect to blood pressure at follow-up, this sample size would be sufficient (85% power, 2-sided 5% alpha) to detect differences between the two groups of 0.42 standard deviations. For standard deviations in diastolic blood pressure of about 9 mmHg, this corresponds to differences between groups of about 3.2 mmHg. There is good evidence from RCTs that a difference of 5 to 6 mmHg in diastolic blood pressure leads to a reduction in stroke of 38% and in coronary heart disease of 16%.[5,37]

5.11 Randomisation

5.11.1 Sequence generation

Eligible study participants were stratified by age and sex and allocated to the intervention and control groups by using computer-generated random numbers. Because of the risk of imbalance in prognostic characteristics that can occur by chance with simple randomisation or block randomisation, we performed stratified randomisation by general practice as well as by age and sex.[239]

5.11.2 Allocation concealment and implementation

I collated an anonymised list of study participants, which only contained patients' initials, their age group, sex and the name of the general practice from which they were recruited. Separate lists for every practice were passed on to Tim Peters, who as a member of the research team was not involved in practice and patient recruitment and who then generated the randomisation sequence.[240] Based on this sequence, I printed separate data collection sheets, which were clearly marked either 'intervention' or 'control'. These data collection sheets were subsequently sent to the practice nurses.

5.12 Blinding (masking)

In this open RCT both the study participants and the practice nurses became aware of the group assignment at completion of the baseline period.

5.13 Data collection and management

I had the ultimate responsibility for data collection, storage and processing. The practice nurses were repeatedly informed about the importance of accuracy in collecting the data to provide high quality information. The data collected for this trial aimed to answer the key questions outlined before and were kept to a minimum.

5.13.1 Data collection

At each appointment, the practice nurses collected data and entered these onto a specially designed data collection form (Appendix 5). This form allowed entering patient data as well as process data of relevance to the study. In addition, further data were collected from the practice nurses using a separate questionnaire. Missing or

incomplete data were collected in personal or telephone interviews with the participating practice nurses or their respective practice managers.

Study participants were asked to bring the electronic monitors with them on every visit to the practice nurse. The practice nurses downloaded data from the electronic monitors onto a personal computer in the consulting rooms using an electronic device called a communicator (Appendix 7), and adherence data were stored on a personal computer in the treatment room using PowerView® software.

5.13.2 Data processing

I collected the data sheets from each practice after the last follow-up appointment. Data from the electronic monitors were downloaded from the practice computer and stored on a floppy disk. Patient and practice data were coded and entered into a Microsoft® Access database as soon as they were received. Ideally, data should have been entered twice by two different people to detect inconsistencies and identify queries, but this was not feasible given the scope of this research project. Data from the electronic medication monitors were transformed into a Stata® database.[241] All data were backed up every night and stored on a secure off site network server.

5.13.3 Data cleaning

Before the analysis all the data were examined with logical, range and coding checks to identify inconsistencies and outliers. All extreme or for any other reason suspicious values were checked against the original data forms.

5.13.4 Confidentiality

At all times all data collected from patients and practice nurses were treated as confidential, since this trial used individual patients' data.[242] Original data sheets were stored in a locked cupboard in a locked office according to regulations set out in the Data Protection Act 1998. All patient data were anonymised prior to the analysis.

5.14 Outcomes

The outcomes for this trial were chosen at the planning stage of the trial and were largely determined by the nature of the trial and the research question.[243] Although this trial has been described as a pragmatic trial, it is relatively close to being an 'explanatory' trial, for which a single main outcome may have been appropriate. For

clinicians and other healthcare decision makers it was, however, important to add information in terms of additional outcome measures to help them weigh up the benefits, risks and costs of the adherence support intervention. Ideally, further outcomes should have included functional status, satisfaction with management and treatment, subsequent use of health services as well as long-term outcomes such as cardiovascular morbidity and mortality. These outcomes, however, were not included for practical reasons in terms of study duration and sample size. There is also an increased risk of reaching statistical significance by chance alone if multiple outcomes are being used, and Peto and colleagues have argued that large trials in particular should focus on a small number of simple outcomes.[244]

5.14.1 Description of terms relating to electronic monitoring

This section gives a brief overview of the different terms and definitions used when measuring adherence with electronic monitoring, which includes the terms that are important for understanding the way electronic monitoring works and definitions of the calculated results that are displayed in the summary provided by the PowerView® software. PowerView® can be used to summarise data generated by the electronic monitors and produce data summary sheets for individual patients. It can generate data tables that can be transformed into different database formats and analysed using statistical software packages.

Electronic monitor

The main tool in measuring adherence in this trial was the electronic monitor. An electronic monitor consists of a container similar to traditional drug bottles and a larger lid, which holds a microchip and a pressure release system (see Appendix 7). This system is activated each time a monitor is opened and closed, called a medication event (see next paragraph). The monitor stores the exact time and date of each opening sequence, and summary data can be downloaded onto a personal computer. Results based on electronic monitoring have been reported in over 350 publications, including over 50 peer-reviewed original research papers, and have a failure rate of less than 1%.[67]

Medication event

The medication event is an electronically detected, time-stamped manoeuvre made by the electronic monitor, which is a necessary condition for removing a dose of a drug. In

practice, this is assumed to designate the taking of a prescribed drug dose. The software allowed manual exclusion of events. In this study events were not taken into account in the calculations in certain circumstances, for example if the monitor was opened during a consultation or when a participant made a note that the monitor was opened for a reason other than taking the medication. An excluded event was never deleted and could be undone at any time.

Dose taken

An event saved in the electronic monitor corresponded to a prescribed dose taken and was created by an opening and closing of the monitor cap. If the monitor stayed open for more than two hours, the programme generated a new event when closing occured. If the monitor recorded two events in an interval of less than 15 minutes, only the first event was taken into account. The second one was filtered on the assumption that the second event represents the patient having mechanical difficulties with the closure.

Start of the dosing day

The dosing day did not start at midnight, because we assumed that some participants might have taken doses at around midnight, perhaps slightly before or after. This could have created different daily dose counts and might have given the impression of rather erratic dosing, when in fact these differences were only due to a few minutes of day-to-day variation. We therefore designated the start of the dosing day to a time when dosing was least likely to occur, which for most people would be 03:00h in the morning. However, this time may not have given the best results for patients who worked night shifts or other unusual hours, so the 03:00h start was a default that was changed for individual patients. It is worth noting that shifting the start of the dosing day from midnight to 03:00h did not alter the basic data.

Observation periods

These were periods defined by the appointment dates with the practice nurse. Observation period one was used to describe baseline adherence, and observation period 2 defined adherence during the follow-up period (see Table 2).

Table 2 Observation periods used for calculating adherence

Observation period	Description
1	Baseline period, that is, the time between the initial appointment and the intervention appointment
2	Time between intervention appointment and final follow-up at six months

Non-monitored periods

If participants were unable or unwilling to use the electronic monitor for a specified period, these so-called non-monitored periods could be defined by their dates and were excluded from all calculations. Unlike the event exclusion where only single events were not taken into account, more of the events in the non-monitored period were taken into account, and the duration of the non-monitored period was subtracted from the observation period.

5.14.2 Ethical considerations relating to electronic monitoring

One important question at the planning stage of this trial was the extent to which information about electronic monitoring should be given to trial participants.[245] There is some evidence from a short-term study of the use of inhalers that covert monitoring yielded superior data compared to conventional approaches where study participants were aware of being monitored.[246]

However, we decided to inform all study participants that during the course of the trial medication adherence would be monitored and that the purpose of the trial was not to identify individual patients' performance, but rather to produce high quality generalisable knowledge. We also emphasised that this study aim was of mutual interests to study participants and investigators. In addition, we pointed out that the individual level of adherence would not be disclosed to the practice nurses or GPs without permission by the study participants.

In most studies that used electronic monitoring, patients have been informed that the medication monitor counts and keeps a log of their medication doses.[132] A study by Cramer and colleagues has shown that dosing patterns, perhaps surprisingly, have not been shown to be influenced by patients' knowledge that medication monitoring is occurring.[247] The practice nurse handing out the electronic monitors in this trial was

asked to tell participants that the electronic monitor would gather data on medication taking patterns, without putting too much emphasis on how exactly the monitor works. She also provided participants with an information sheet on how to use the electronic monitor (see Appendix 8).[98]

One may argue that adherence may not always be beneficial and that not all strategies to increase adherence to medication are in the patients' best interest.[248,249] Although promoting and measuring adherence within a clinical trial can have potential risks as well as benefits, we felt that on balance these risks, that is, an increased incidence of adverse effects, were indeed small and did not affect the ethical issues around autonomy and privacy substantially.

5.14.3 Definitions of adherence

As highlighted in Chapters 2 and 3, adherence has been defined in different ways. When using electronic monitoring for outcome measurement of adherence, the following definitions are the ones that are most commonly used.

Timing compliance

Timing compliance is the strictest of the adherence measures described here and was the main outcome used for this trial. It can be defined as the percentage of the prescribed number of doses taken within a correct interval. The correct interval between two doses is determined by the prescribed drug regimen. For a regimen with one dose per day the correct inter-dose interval is 24 hours, for two doses per day it is 12 hours, and for three doses a day it is eight hours. Allowing for a tolerance of ±25%, for a regimen of one dose a day the correct inter-dose interval is between 18 and 32 hours. The percentage of doses taken within a correct interval is the number of correct inter-dose intervals divided by the total of doses taken less one, because there is one less interval between doses than the total number of doses taken.

Correct dosing

'Correct dosing' is the percentage of days on which the correct number of doses was taken.

Taking compliance

Taking compliance is the number of doses taken divided by the number of doses prescribed during the monitored interval. The number of doses prescribed corresponds with the number of monitored days multiplied by the number of doses prescribed per day and provides the equivalent data to a 'pill count'. This adherence measure is the least strict of the three described so far.

Therapeutic coverage

The therapeutic coverage corresponds to the percentage of time that the patient has maintained therapeutic drug action, given the measured or assumed value for duration of action and the measured inter-dose intervals. A therapeutic coverage of 100% signifies that all inter-dose intervals are shorter than the duration of action. It decreases as the number and the duration of intervals longer than the duration of drug action increase. Although the therapeutic coverage appears to be a valuable additional measure of adherence, it has not been used for this study. The main reason for is that drugs used in the electronic monitors varied between participants and have different pharmacological properties including half-lives, and the exact durations of action for many drugs that were used in this study are not known.

5.14.4 Primary outcome

The primary outcome with respect to the effectiveness of the intervention was timing compliance in the six months period following the intervention, controlling for adherence in the baseline period (see Figure 10 for study timeline and Table 2).

5.14.5 Secondary outcomes

Adherence

Secondary adherence outcomes were the two less strict measures of adherence, correct dosing and taking compliance as defined above.

Blood pressure

The main secondary outcome used in this trial was blood pressure. At each visit, the practice nurses measured systolic and diastolic blood pressures according to the British Hypertension Society guidelines and an evidence based review by McAlister & Straus

(Figure 1).[19,250] Since practices used different methods for checking the blood pressure, that is, manual or automatic devices, we asked the practice nurses to use the same measurement instrument for each patient during the study, whichever was the preferred system at that time. Since we were calculating the differences in blood pressure levels at follow-up, adjusted for baseline values, any differences between results from manual and automatic blood pressure readings can assumed to be negligible.[251]

5.15 Statistical analysis

The statistical analysis was conducted according to an analysis plan that was agreed before the start of the analysis. Data were analysed using Stata version 8.[241] Baseline comparability of the groups in terms of cardiovascular risk factors, age, sex, medication usage and treatment duration was investigated by using descriptive statistics. Process measures were evaluated in terms of non-attendance at follow-up between the groups and the extent to which the practice nurses followed the protocol for the intervention. The distributions of the main outcome variables and residuals were investigated by producing frequency histograms and graphical plots.

We used an intention-to-treat analysis because this helps preserve the prognostic balance in the study arms and reduces the influence of study withdrawals and patients lost to follow-up.[252] The primary intention-to-treat analyses used multivariable regression models, adjusting for the values of the outcome variables at baseline as well as the stratifying variables. By using analysis of covariance, each participant's follow-up score was adjusted for her or his baseline score while still producing p-values and 95% confidence intervals for differences between the intervention and control groups.[253] This analysis compared timing compliance at final follow-up between the intervention and control groups. The influence of missing values was investigated by comparing the intention-to-treat model with a model in which missing values were replaced with the last observation carried forward.

The secondary analyses comprised first additional adjustment in these regression models in terms of any potentially influential variables exhibiting some degree of imbalance at baseline and, secondly, process variables. Subgroup analyses were kept to a minimum because they are unreliable and have a relative high risk of producing false positive chance findings.[254] Pre-planned subgroup analyses were therefore only conducted for age, sex, drug group and total number of drugs prescribed by introducing appropriate interaction terms to investigate differential effects. I included these

parameters in the subgroup analysis because they were either known confounders or were assumed to potentially influence the relationship between intervention and outcome.

The relationship between timing compliance and blood pressure was explored by using scatter plots and calculation of correlation coefficients as well as linear regression models adjusting for the stratifying variables.

5.16 Summary

This chapter described the study methods used for the RCT of nurse-led adherence support in hypertension. It highlighted some of the problems that are associated with research in adherence and discussed the rationale for the sometimes difficult decisions that were made at each stage of the trial, from the planning phase to the final analysis. The following chapter describes a study comparing an adherence self-report tool with electronic medication monitoring, and the trial results will be presented in Chapter 7.

6 Comparison of an adherence self-report tool with electronic medication monitoring

6.1 Introduction

In this chapter I describe the methods and results of a study that validated a newly developed adherence self-report tool aiming to predict adherence to blood pressure lowering medication.

As outlined in Chapter 2, a variety of measurement tools are available to assess patient adherence to medication. Many of these instruments have disadvantages and often produce results of doubtful validity. The method that comes closest to a 'gold standard' is electronic monitoring, but due to costs this method has mainly been used as a research tool and is at present not suitable for use in day-to-day clinical practice.

The simplest method of measuring adherence in clinical practice is self-report, as it can be easy to use, is non-invasive and relatively quick. However, there is a common perception among health professionals that patients do not always tell the truth about their medication taking. Hippocrates wrote:

> *"Keep a watch also on the faults of the patients, which often make them lie about things prescribed" (Hippocrates, 5th century BC)*[14]

Although studies in the past decades have appeared to confirm this perception,[255,256] recent evidence has shown that this view may be outdated, and self-report scores of adherence have been shown to be useful in the primary care setting.[2,257] To date, only a few adherence questionnaires are available, and even less have been validated with more objective methods of measuring adherence.[89,90,257]

In the following sections I describe the development and subsequent validation of a new adherence self-report tool, which has been designed on the basis of previous research.

6.2 Background

Patients are often reluctant to admit non-adherence to health professionals.[2] However, accurate information about patient adherence to medication can be useful for health professionals to target interventions more effectively and efficiently, particularly if non-response to pharmacological treatment is present.[172,258] Horne and colleagues developed

and evaluated a new method for assessing the cognitive representation of medication, the Beliefs about Medicines Questionnaire.[123] This study showed that this method was useful in assessing beliefs that patients commonly hold about the medicines that they are being prescribed for a particular condition and about medicines in general. This method, however, is more useful for research into patients' perspectives of treatment rather than to assess adherence to treatment in day-to-day clinical practice.

Ogedegbe and colleagues recently developed and evaluated a 26-item medication self-efficacy scale.[259] The authors aimed to identify situations in which patients have low self-efficacy, which is a known predictor for a wide range of health behaviours. This scale showed good internal consistency and stable scores, and it was easy to use and understand for patients. However, it is unclear how applicable this scale would be for UK primary care, as it has only been evaluated among African-Americans in the US. This study did also not determine how well this scale predicts adherence to prescribed antihypertensive medications and blood pressure control.

Self-report of adherence appears to be a flexible and practical method for assessing adherence, but there are concerns about their ability to detect true non-adherence. The sensitivity of self-report adherence measures was below 60% in a number of studies published in the past decades, indicating false negative results for at least 40% of people with true non-adherence.[86,97,255,260-263]

Despite this somewhat discouraging outlook, the development of adherence self-report tools has become a focus of interest again in recent years, and two studies used electronic monitors to validate newly developed adherence self-assessment tools.[89,90] Svarstad and colleagues designed a Brief Medication Questionnaire to screen for adherence and barriers to adherence.[89] Their tool includes a 5-item Regimen Screen asking patients how they took their medicines in the past week, a 2-item Belief Screen asking about drug effects and bothersome features, and a 2-item Recall Screen about potential memory difficulties. The validity of this instrument was assessed in 20 patients who were prescribed ACE inhibitors by using electronic monitors (MEMS®) as a comparator (see Section 2.4.4). Their results showed 80-100% sensitivity for different types of adherence, suggesting that this tool is more sensitive than existing instruments. This study was the first to demonstrate that sensitivity levels vary by type of non-adherence and type of screening tool.

De Klerk and colleagues developed a new adherence questionnaire for use in rheumatology.[90] This questionnaire aimed to measure adherence and identify factors

that contribute to sub-optimal patient compliance in 127 patients with rheumatoid arthritis (RA), polymyalgia rheumatica (PMR), and gout, using MEMS® for comparison. This study showed a sensitivity and specificity to detect what the authors described as "good taking compliance" of 62% and 95%, respectively.

A study by George and colleagues investigated the value of four different methods of assessment of adherence in patients in UK primary care who were prescribed tricyclic antidepressants.[257] They found that electronic monitoring was the most informative technique, but that self-report using a scale developed by Morisky and colleagues proved a useful screening technique with a sensitivity of 72.2% and a specificity of 74.1% for detecting ≥80% adherence.

Although the results of these studies are promising, it is difficult to know how generalisable they are to people on blood pressure lowering medication, because two of these studies were targeted at symptomatic patients with rheumatic disease or depression,[90,257] whereas the other was small with only 20 study participants.[89]

In addition, most of the self-report tools described above appear to address two aims at the same time, that is, to establish (a) whether non-adherence is present or not and (b) the reasons for non-adherence. There are two main disadvantages of this combined approach for use in clinical practice. First, the number of issues increases, which adds to the time needed for completion, and second, many questions are redundant for patients who take their medicines regularly and do not have any problems.

The study described in this chapter focuses on the first question, that is, whether non-adherence is present or not. If this question can be answered quickly, then patients who have problems with taking medicines can be given the opportunity to talk about any problems with the health professional in a similar way as described in the adherence support intervention (see Chapter 5). If patients do not have any problems with their medication, then both the patient and health professional can centre their attention on other reasons for non-response to pharmacological treatment. The aim of this study was, therefore, to develop a new short self-assessment tool that could be used as a brief screening tool in a busy clinic.

6.3 Methods

6.3.1 Objective

The objective of this study was to validate a newly adapted adherence self-report tool aiming to predict adherence to blood pressure lowering medication against electronic monitors (MEMS®) as the comparative 'gold standard' in uncontrolled hypertensive patients in a primary care setting.

6.3.2 Design of the adherence self-report tool

The design of this adherence self-report tool is based on an instrument that has been developed by de Klerk and colleagues, who used six descriptions of patients with different levels of adherence.[264] Patients were asked to indicate which of these fictitious patients would describe them best (Figure 11 below).

Figure 11 Patient descriptions used in patients with rheumatic diseases

Instruction	**Below you find six descriptions of six different patients. Try to indicate which of the descriptions describes yourself best. It is possible that only part of the description describes you. In that case, try to select the description that is most appropriate for your situation. Where the description says 'he' you can of course also read 'she'**
Patient 1	Patient 1 is very punctual in everything he does. He gets up every day at the same time, eats at the same time, and takes his drugs at the same time. There is never more than 15 minutes difference in the time of taking the drug. Forgetting to take the medicines never occurs.
Patient 2	Patient 2 is also very punctual but somewhat less so than patient 1. Every now and then he deviates a little from the daily routines. He takes essentially all medicines, but the timing with which he takes them may vary a little. Very infrequently, for example twice a month, he forgets to take his anti-rheumatic medicines.
Patient 3	Patient 3 is less punctual. He likes change. He also does not want to have his life dictated by his disease or medicines. He is also less punctual in taking his medicines. He takes most of the prescribed tablets, but the timing varies, and it happens every now and then, consciously or unconsciously, that he skips a scheduled dose (approximately six times per month)
Patient 4	Patient 4 does not care much about his medicines. There may be many causes for this, like inactive disease or other things that require attention. Therefore there is not much regularity in taking the drugs, and it happens often that he does not take the medicines (approximately 15 times per month)
Patient 5	Patient 5 does almost not take any of the medicines prescribed by his rheumatologist. Sometimes there is a period in which he takes a couple of tablets, but overall there are more days when he does not take any drugs than when he does.
Patient 6	Patient 6 denies being ill. The rheumatologist may say that there is something wrong, but he does not agree with that at all. Of course, this has consequences for taking the drugs, as these are almost never taken.

Source: de Klerk et al., J Rheumatol 1999;25:2635-41.[264]

These patient descriptions were based on about 40 patient interviews, past research and analyses of various datasets of patients with rheumatic diseases, which were obtained using MEMS®.[264] Patients identifying with description one or two were classified as 'compliant', whereas descriptions 3 to 6 were regarded as 'non-compliant'. These patient descriptions were used as a 'surrogate gold standard' for the development of a

questionnaire to explore the likelihood and underlying factors for variable patient compliance on antirheumatic drug therapy, but no data on sensitivity or specificity were provided. I adapted these patient descriptions as described below to develop a tool for quick assessment of adherence in a clinic setting.

Planning

When using structured questionnaires or self-report tools it is important that both the researchers or health professionals and patients have a similar theoretical frame of reference and interpret the contents of the tool in question in the same way.[265] The aim of altering the above patient descriptions was to make them even simpler, while being aware of the effects that changes in the wording could have on the type of responses patients might give. This was done with permission from the developers of the original scale.

The planning stage involved a review and simplification of the tool. The descriptions were shortened and the format of the one-page form designed. The response format (that is, a dichotomised answering frame in terms of a yes/no response) was kept, assuming that each item meant the same to each study participant. The advantage of this pre-coded response was that it was relatively easy to analyse. However, we were aware that the given responses may have forced participants to give inappropriate answers. There was also a risk of these questions prompting participants to give a certain 'desired' answer, leading to social desirability bias.[265] This we hoped would be pre-empted by careful wording of the instructions.

We decided to use the self-report tool in participants who were recruited to the trial described in Chapters 5 and 6. The most appropriate timing for administering this self-assessment tool appeared to be the beginning of the run-in phase (see Figure 10 on page 78). During this run-in phase, all study participants used electronic monitors for a baseline assessment of timing compliance for about 30 days, and the data obtained with the self-report tool would be validated with the data obtained from the electronic monitors. Allocation to the treatment groups was revealed and came into effect at the end of this run-in period.

Piloting

After refining the wording in the self-report tool, we tested the self-report form on researchers and other members of staff. The contents were further discussed with the

participating practice nurses and some patients. Main issues of interest were the layout, whether the wording was easy to understand, whether all reasonable alternatives were included and how people generally felt about the form. Constructive comments received during this process were used to further develop and pilot the form. The final version was approved by the South & West Multi-centre Research Ethics Committee.

Figure 12 Summarised contents of the self-assessment tool

Please find below six examples of how some people describe how they take their medication. We would be grateful if you could tick the one description that you feel comes closest to describe how you take your blood pressure tablets:	
Level	Description
1	"I always take all of my tablets at the same time of day".
2	"I manage to take all my tablets – but not always at the same time of day".
3	"I sometimes do not take all of my tablets, knowingly or unknowingly, but never omit more than one dose at a time".
4	"I miss many tablets and about three to four times a year I miss my tablets, knowingly or unknowingly, for two or more days".
5	"I miss many tablets, knowingly or unknowingly, and at least once a month I miss my tablets for two or more days".
6	"I take hardly any of my blood pressure tablets".
We are not looking for a particular answer and would be grateful for an honest response. PLEASE TICK ONLY ONE BOX. Neither the researchers nor your practice nurse will in any way mind what answer you give.	

6.3.3 Patient recruitment

The study population consisted of patients who were recruited for the RCT described in Chapters 5 and 6 (for details about the recruitment process please refer to Section 5.6).

6.3.4 Completion of the self-report tool

The study participants were asked to complete the adherence self-report tool at the beginning of their first appointment with the practice nurse. The practice nurses were encouraged not to discuss the contents of the questionnaire or the answers that patients had given.

6.3.5 Analysis

I analysed the data using Stata Version 8.[241] The analysis used multivariable regression models, adjusting for the stratification variables age, sex and practice, which were the stratifying variables in the trial. Pre-planned subgroup analyses were conducted for age, sex, and the total number of drugs a patient is taking by introducing appropriate interaction terms to investigate differential effects. These variables were chosen because of their potential effect on the answers given in the self-report tool.

Although previous studies that used MEMS® to validate self-assessment tools calculated sensitivity, specificity and predictive values,[89,90,257] it was decided not to calculate these test parameters because this would have required reducing timing compliance and/or the answers from the questionnaire into binary variables, that is, 'adherent' and 'non-adherent'. Timing compliance is a continuous variable and the results of the completion of the self-assessment questionnaire provide ordered categorical data. Although many studies have used artificial cut-off points to define adherence (for example, 80% or 90%), these are often meaningless and very much depend on the particular drug being used (see also Sections 3.6.3 and 4.3)[132,134,266]. For this reason, multivariable regression analysis appears to be the more appropriate approach to compare the adherence self-report tool with electronic monitoring.

6.4 Results

Of 837 eligible patients with uncontrolled hypertension, 249 attended the first appointment and entered the 30-day run-in period (see CONSORT trial flow, Figure 15). Four patients dropped out during the run-in period (one died, one became unwell, one moved away, and for one the reason was not known). Of the 249 participants entering the run-in period, 235 (94.4%) completed the self-report questionnaire. All participants for whom data were missing showed more than 80% timing compliance.

6.4.1 Baseline characteristics of patients

Details about the baseline characteristics of the study participants can be found in Section 7.2.4. Out of 235 participants who completed the questionnaire, 161 (68.5%) identified themselves with the first patient description ('perfect adherence'), 45 (19.1%) with the second, and 26 (11.1%) with the third. The numbers in the subsequent patient descriptions were very small (Table 3). Patient descriptions four to six were, therefore,

combined with description two for the analysis, which raised the number of participants in this group from 26 to 29 (12.3%)

Table 3 Numbers of participants who identified themselves with the six patient descriptions (levels 1 to 6) in the self-assessment tool

Level	Number of participants	Per cent
Level 1	161	68.5
Level 2	45	19.1
Level 3	26	11.1
Level 4	2	0.9
Level 5	1	0.4
Level 6	0	0

Table 4 presents key baseline characteristics for these three groups. There were no important differences in terms of blood pressure, age, or sex between the three levels. In the 10 participants who did not complete the self-assessment questionnaire, mean baseline timing compliance was 93.6% ± an SD of 7.3%, with a mean systolic blood pressure of 154.8 ± 14.1 mmHg and a mean diastolic blood pressure of 88.4 ± 8.7 mmHg.

Table 4 Key baseline characteristics for study participants identifying themselves with one of the first three patient descriptions (adherence levels) on the self-assessment tool

	Level 1 (n=161)	Level 2 (n=45)	Level 3 (n=29)
Baseline systolic blood pressure in mmHg, mean ± SD	150.2 ± 17.6	148.6 ± 13.0	151 ± 15.3
Baseline diastolic blood pressure in mmHg, mean ± SD	82.6 ± 9.7	84.3 ± 8.3	85.1 ± 10.3
Age in years, mean ± SD	68.5 ± 9.2	66.6 ± 10.8	67.6 ± 11.8
Per cent men	55.3 (89/161)	57.8 (26/45)	44.8 (13/29)

6.4.2 Analysis

The 'gold standard' used for the analysis was timing compliance, which is the percentage of a prescribed number of doses taken in a specified correct interval. Table 5 presents the mean timing compliance for each level that study participants identified themselves with on the self-assessment tool and the respective 95% confidence intervals. These results show that from one level to the next lower down the timing compliance measured through MEMS® dropped by about 5% per level.

Table 5 Timing compliance for each level of the adherence self assessment tool with 95% confidence intervals

Level	Level 1	Level 2	Level 3
Mean timing compliance (%)	94.8	89.6	84.7
95% CI	93.3 to 96.3	83.4 to 95.8	76.5 to 92.8

Table 6 presents the results of a regression model of the relationship between the results of the adherence self-report tool and the corresponding mean timing compliance. Participants identifying themselves with patient description (Level) 2 had on average 5.8% (95% CI: 0.6% to 10.9%) lower timing compliance than those who identified themselves with level 1. Participants who identified their pattern of medication taking with level 3 had on average 5.0% lower timing compliance than those who identified themselves with level 2 (95%CI: -2.0% to 12.0%). Thus there is strong evidence that a drop in one level from level 1 to level 2 and from level 2 to level 3 is associated with a decrease in timing compliance of about 5% (p=0.0004).

Table 6 Regression model of the relationship between the results of the adherence self-report questionnaire and timing compliance, adjusted for age, sex and practice

	Difference in timing compliance (%)	95% confidence interval	p-value [a]
Level 2 versus level 1	5.8	0.6 to 10.9	0.0004
Level 3 versus level 2	5.0	-2.0 to 12.0	

[a] 2 df

6.4.3 Additional analyses

Supplementary analyses were planned at the protocol stage and finalised in the study protocol before the trial was analysed. These analyses considered whether there is any evidence that a trend in mean timing compliance across the levels is different across, for example age, sex, or the total number of drugs a patient is taking. The following tables show the differences in timing compliance for the different levels that participants marked in the self-assessment questionnaire for these different groups of participants. There was no evidence for a differential effect for any of the variables that were investigated in these analyses. However, there is a difference of more than five percentage points for timing compliance in level three between the two age groups, which could suggest a possible differential effect for age. There is also a difference of 11 percentage points in level three for the number depending on total drug usage (Table 9). It is important to appreciate that this type of analysis has limited power and does not necessarily exclude an interaction if there is one.[254] Interestingly, results from Table 9 lead to the hypothesis that Level 3 participants on six or more drugs may have higher timing compliance than those on fewer oral drugs.

Table 7 Mean timing compliance (% ± SD) for the different self-report levels, stratified by age

Age group	Level 1	Level 2	Level 3	p-value [a]
Under 60	95.4 ± 8.6	91.1 ± 10.1	80.8 ± 12.7	0.31
Age sixty and over	94.6 ± 8.5	89.1 ± 19.0	86.2 ± 19.7	

[a] Test for interaction

Table 8 Mean timing compliance for the different self-report levels, stratified by sex

Sex	Level 1	Level 2	Level 3	p-value [a]
Men	94.2 ± 9.4	91.0 ± 14.8	84.1 ± 20.5	0.50
Women	95.6 ± 7.0	87.4 ± 20.5	85.2 ± 19.9	

[a] Test for interaction

Table 9 Mean timing compliance for the different self-report levels, stratified by the total number of oral drugs

Total number of oral drugs	Level 1	Level 2	Level 3	p-value [a]
1 to 2	95.6 ± 4.7	87.9 ± 21.9	75.5 ± 8.4	0.27
3 to 5	93.7 ± 10.4	93.1 ± 8.0	86.9 ± 23.5	
6 or more	94.6 ± 8.8	80.8 ± 28.1	89.7 ± 7.2	

[a] Test for interaction

6.5 Discussion

Electronic medication monitoring would in theory be a useful method to screen for non-adherence, but its application as a screening tool is largely limited by its costs. Self-report of adherence is much simpler, and this study aimed to validate a newly developed adherence self-report tool against data obtained by electronic monitoring in hypertensive participants recruited for the RCT.

6.5.1 Interpretation of findings

This study showed that a brief self-report tool based on six patient descriptions could predict adherence to medication in patients taking blood pressure lowering medication. A drop to a lower level (that is, from level 1 to level 2 or from level 2 to level 3) was associated with a decrease in timing compliance of around 5%. Because most study participants showed high levels of adherence, it is difficult to know how this tool would perform in people with lower levels of adherence. There is strong evidence to suggest that the self-report tool described in this thesis can to a certain extent predict adherence levels in patients with high blood pressure. The self-report tool appears to perform well irrespective of the number of drugs taken, which is an important issue as suggested in our systematic review described in Chapter 3.

6.5.2 Discussion of findings in the light of previous research

This study confirms the findings from previous studies that self-assessment tools can to a certain extent detect non-adherence to prescribed medication. [86,89,90,257,264] However, the self-report tool described in this study was different to most previous research in that it only aimed to focus on the question whether non-adherence is present or not, rather than establishing the reasons for non-adherence. This tool is also considerably

shorter than most other self-assessment questionnaires, which perhaps makes it more suitable for use in a busy primary care or hypertension clinic.

Consistent with high timing compliance in the study sample, study participants identified themselves with one of the first three patient descriptions, ranging from 'perfect' adherence to 'occasionally missing a tablet', which could limit the generalisibility of the results to patients with lower adherence. Nevertheless, our results are remarkably similar to findings in a non-trial popoulation by de Klerk and colleagues, who found that patients with rheumatological conditions also showed high self-perceived adherence rates, with patient descriptions 1 to 3 being used by the majority of patients.

As well as the RCT described in this thesis, most previous studies used only one electronic monitor per participant. This assumes that the results obtained for the drugs used in the monitor are representative of compliance levels for other drugs. The results in Table 9 are surprising and raise the possibility that this adherence self report tool could be superior to electronic monitoring, in that it takes account of all the drugs a patient is taking rather than a single drug. However, on current evidence this statement is speculative and further studies are required for it to be substantiated.

6.5.3 Limitations of this study

Baseline timing compliance was high in this study, which suggests the potential for response bias, as patients with lower adherence levels were perhaps less likely to take part in this study. Unfortunately, due to data protection reasons we were unable to obtain data on eligible patients who refused to take part, which would have allowed us to investigate any systematic differences between these individuals and the study participants.

We do not know how the results of this study may have been affected by variations in the behaviour of the practice nurses and their reactions or attempts to influence the behaviour of the patients.

6.5.4 Implications for practice

This study has shown that a brief adherence self-report tool can be effective in screening for suboptimal adherence in hypertensive patients. Patients were able to complete the self-report tool quickly, and in future the results could be used immediately for patient and health professional to discuss any problems with medication taking. The main

implications for practice relate to the distinction between non-adherence and non-response to medication, which can be difficult and sometimes impossible in clinical practice. If patients do not have any problems with their medication, then they would not waste any time in completing long questionnaires and can together with the health professional focus their attention on other reasons for non-response to pharmacological treatment. Because of its brevity and simplicity, this self-assessment tool could be used routinely in the assessment and review of all hypertensive patients. The above results support the use of this tool in the routine assessment and review of hypertensive patients, although they require further evaluation and validation. It is worth bearing in mind that detection of poor adherence does not always relate to inadequate control per se.

6.5.5 Implications for future research

Further research is required to investigate the validity of this self-report tool in patients with lower adherence levels and in a non-trial population. More evidence is needed to predict future adherence levels and to determine the best method to administer this self-report tool. Future studies should evaluate this tool in different clinical settings and in different medical conditions.

6.6 Summary

This chapter described a study comparing an adherence self-report tool with electronic medication monitoring. This study showed that a brief self-report tool based on six patient descriptions could predict adherence to medication in patients taking blood pressure lowering medication. Patients identifying themselves with levels 2 or 3 had 5% and 10% lower timing compliance as measured by MEMS®, respectively, than those participants describing themselves as being 'perfect' adherers. These results confirm the value of MEMS® in measuring adherence and further justify the use of this method in the randomised trial, the results of which are reported in the following chapter.

7 Results of the RCT of nurse-led adherence support in hypertension

7.1 Introduction

This chapter describes the results of a pragmatic randomised controlled trial evaluating the effectiveness of practice nurse-led adherence support. It begins with descriptive statistics of recruitment to the trial in terms of general practices and study participants. I then present the results of the baseline comparability of the intervention and control groups. The main part of this chapter consists of the primary analysis for the adherence and blood pressure outcomes. Following this are the results of secondary and subgroup analyses. Finally, I summarise the main findings of this study.

7.2 Descriptive results

This sections presents descriptive results for the practices and participants in terms of recruitment, participant flow, and other parameters relevant to this study.

7.2.1 Recruitment

Recruitment of practices

Of the 172 practices in what used to be Avon Health Authority, a sample of 82 were contacted and invited to take part in the study, of which 23 (28%) agreed to participate. The main reasons for declining the invitation to take part were workload and staff related. It is worth pointing out here that at the time when this RCT was conducted, there was a national shortage of practice nurses in the UK.[267,268] This led to some practices experiencing major problems in providing treatment room services.

Two practices subsequently had to withdraw their participation. The first practice was a single-handed practice that, because of software problems, was unable to perform a search of the practice computer for hypertensive patients. A second practice had to withdraw after patients had been recruited, because the practice nurse who was conducting the research fell ill and went on long-term sick leave.

Recruitment of participants

A total of 5170 patients in 22 general practices were eligible for recruitment. Of these, the practice nurses and GPs identified 572 patients who did not meet the inclusion criteria or who were considered unsuitable for the study because of illness or personal circumstances. A random sample of 837 patients fulfilling the inclusion criteria was invited to take part in the study (see Figure 15 for the CONSORT flow diagram below). Of these, 371 (44.3%) consented to receive further information about the study, which raises the possibility of this sample being a selected subgroup of the eligible hypertensive patients.[269] Having obtained the study information and a consent form, 326 out of the 371 patients (87.9%) finally consented to take part in the study. Forty-five patients (12.1%) did not return their consent form for unknown reasons. Because patients were initially contacted by the practices, I was not given their names or addresses. For reasons of confidentiality it was not possible to contact those patients to investigate whether they were systematically different from the ones who agreed to take part.

The number of men and women recruited to the study groups in each practice are presented in Figure 13 and Figure 14. The aim of recruiting eight women and men into both intervention and control groups was only fully achieved in two practices, with some differences in recruitment rates between practices.

Figure 13 Number of male participants recruited per practice in both intervention groups

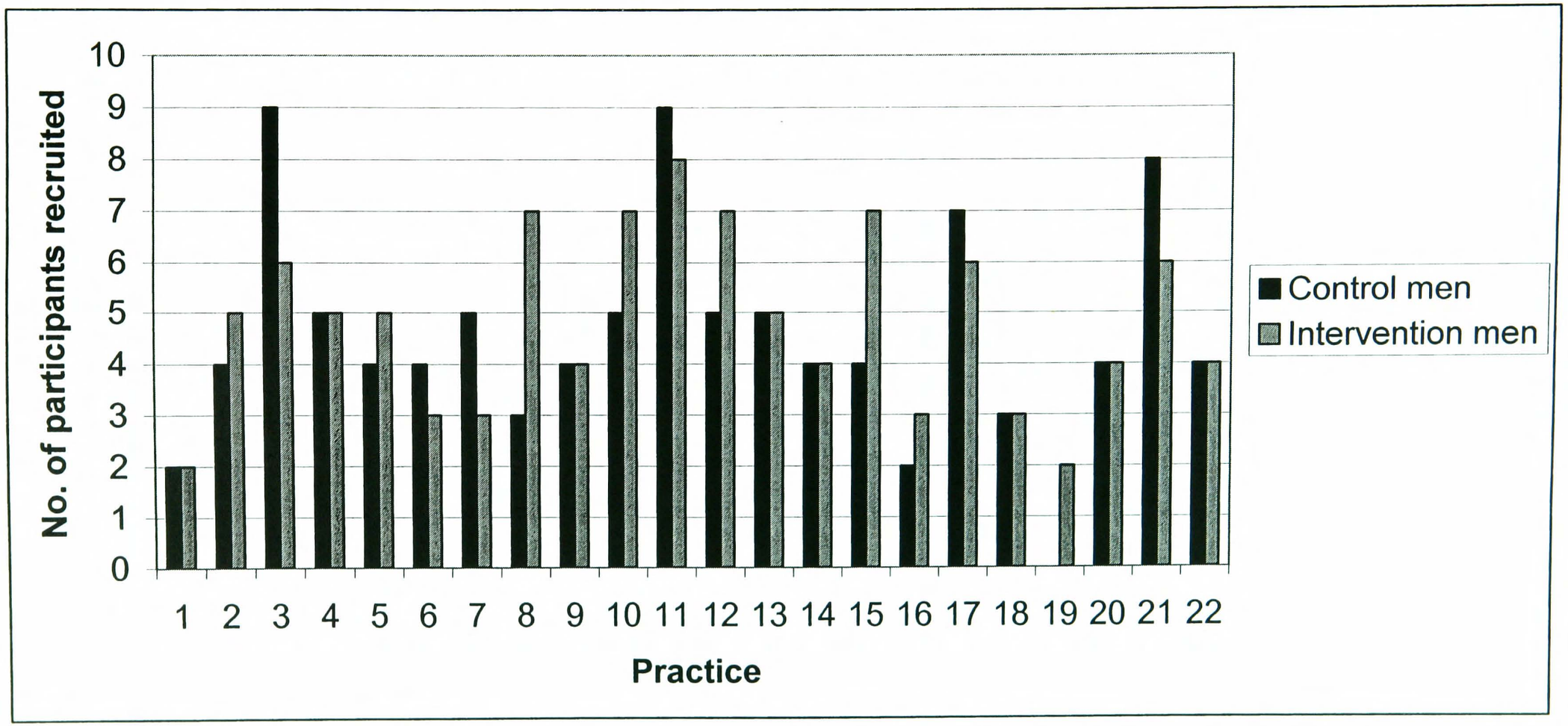
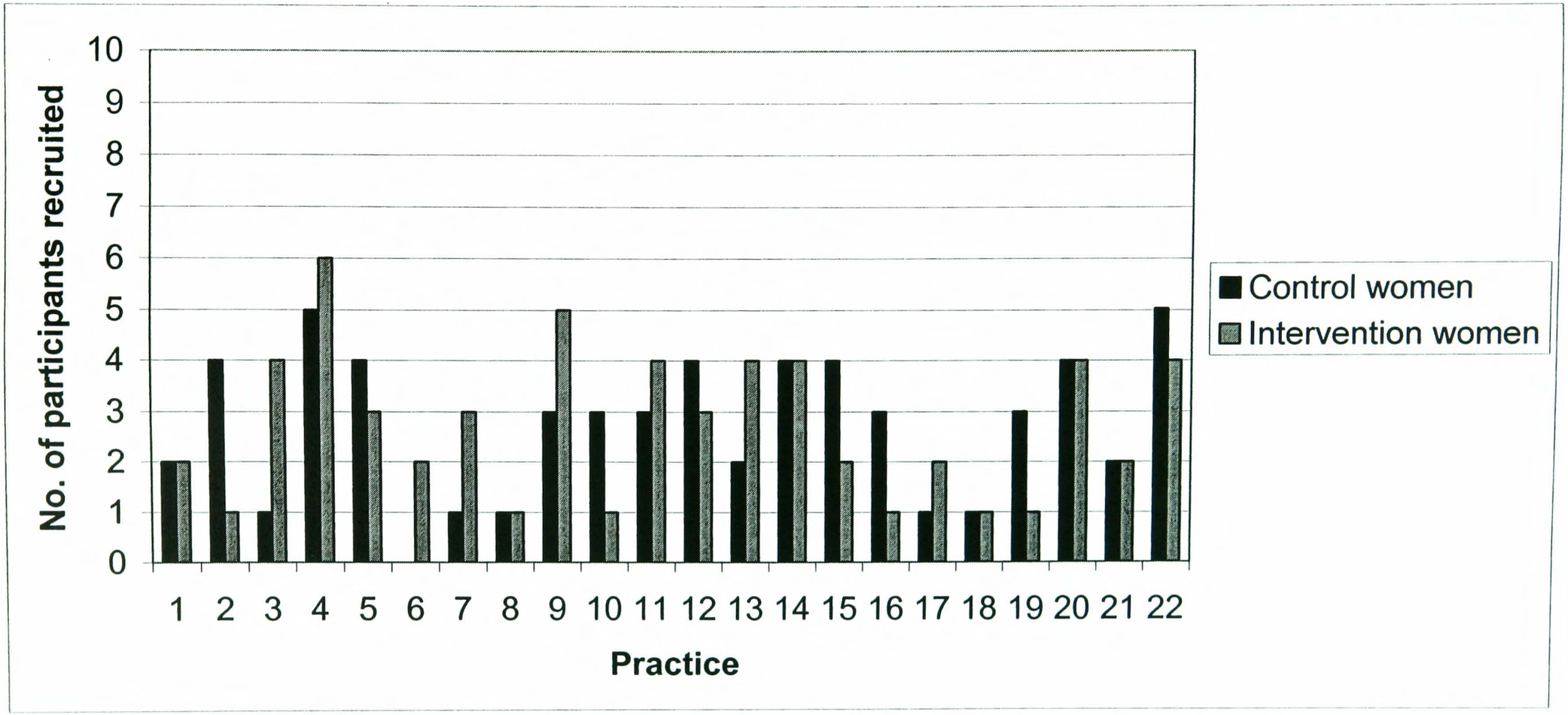


Figure 14 Numbers of female participants recruited per practice in both intervention groups



7.2.2 Participant flow

The CONSORT flow diagram in Figure 15 below provides an overview of the participant flow.[230] Having agreed to receive further information about the study and a consent form, 326 participants returned this and initially consented to take part in the study. Before the first appointment, which was the start of the run-in or baseline period, 77 participants dropped out for reasons given in the flow diagram. Their distribution in terms of the stratifying variables age and sex is presented in Table 10. All of these dropouts were predominantly men (87.0%) aged 60 years and over, with no dropouts in the under 60s group.

Table 10 Dropouts between initial consent and first (baseline) visit by age and sex

	Age <60 years	Age ≥60 years	Total
Men, n (%)	0 (0)	67 (87.0)	67 (87.0)
Women, n (%)	0 (0)	10 (13.0)	10 (13.0)
Total	0 (0)	77 (100)	77 (100)

Figure 15 CONSORT flow diagram

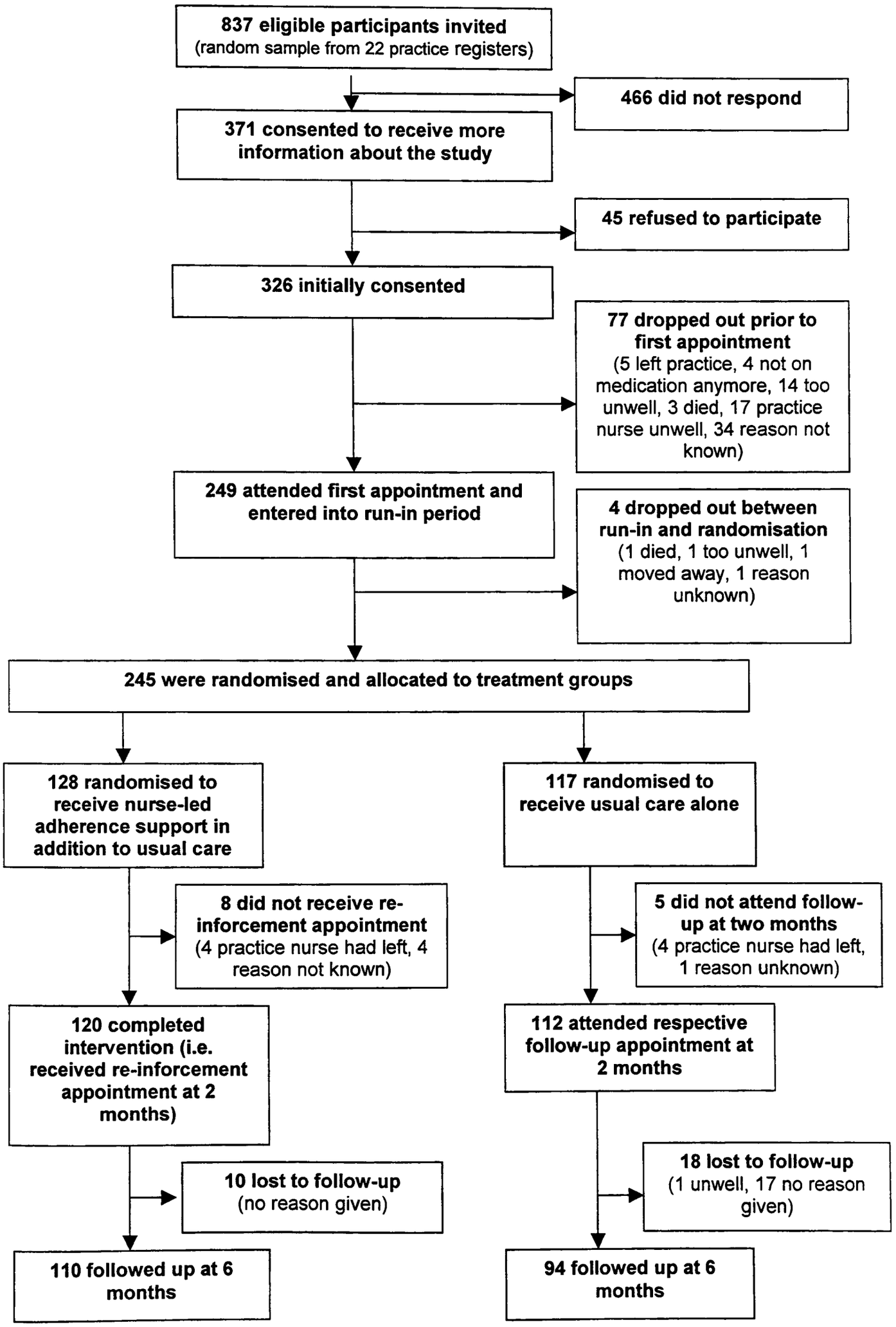


Table 11 shows the numbers and percentages of dropouts between consent and the initial appointment for individual practices. Dropouts at this stage occurred in 14 out of 22 practices (63.6%). Seven or more participants dropped out in six practices.

Table 11 Dropouts between initial consent and first (baseline) appointment by practice

Practice number	Frequency	%	*Cumulative %*
2	2	2.6	*2.6*
3	7	9.1	*11.7*
4	2	2.6	*14.3*
5	1	1.3	*15.6*
8	1	1.3	*16.9*
9	3	3.9	*20.8*
10	4	5.2	*26.0*
11	4	5.2	*31.2*
12	8	10.4	*42.0*
13	2	2.6	*44.2*
15	9	11.7	*55.8*
17	8	10.4	*66.2*
21	9	11.7	*77.9*
22	17	22.1	*100*
Total	*77*	*100.0*	

Four participants dropped out in the run-in period prior to randomisation, of which one died, one was too unwell to take part any longer, one moved away and one did not attend without giving a reason. Table 12 shows the losses to follow-up, which were all men, in the baseline period by practice and age group. A total of 245 study participants were randomised to receive either adherence support (n=128) or usual care (n=117).

Table 12 Losses to follow-up in the baseline period prior to randomisation (only men lost to follow-up at this stage)

Practice no.	Age <60 years	Age ≥60 years	*Total*
6	1	0	*1*
8	0	1	*1*
13	0	1	*1*
19	0	1	*1*
Total	*1*	*3*	*4*

After randomisation and delivery of the first part of the intervention, a total of 13 participants of the 245 who were randomised (5.3%) were lost to follow-up before their first follow-up appointment at two months, with eight (61.5%) in the intervention group and 5 (38.5%) in the control group. More than half of these losses to follow-up were due to a practice nurse having left in one single practice and not passing on responsibility for the study to another nurse.

The differential losses to follow-up after randomisation will be described below in Section 7.3, where I also investigate the effect of process measures on the effect of the intervention, which includes attendance at follow-up appointments.

7.2.3 Characteristics of recruited practices

Comparison with regional and national data (external validity)

Data on list sizes and number of partners of practices taking part in this RCT compared with those in Avon and the UK are provided in Table 13. The data for Avon are based on the 'Avon Practice Comparisons', which were provided by the Avon IM&T Consortium to general practices in 2001. Data for the UK are for 2001 and based on the RCGP Information Sheet No. 2 'Profile of UK Practices'. Since the UK data were derived only from practices falling under the General Medical Services (GMS) contract, these data may not represent practices that have recently changed to Personal Medical Services (PMS).

The overall mean list size in study practices (10,285) was smaller than for Avon practices (13,789). However, the mean number of patients per general practitioner was higher in study practices compared to the national average (2,132 versus 1,841).

Although there appear to be differences in list sizes between the study practices and practices in Avon and in the UK as a whole, these are not excessive and unlikely to affect the external validity of the study.

In terms of the number of principals by size of practice, there were slight differences between study practices and UK practices with respect to smaller practices (0.9% versus 8.5% for single handed and 3.6% versus 12.1% for 2-partner practices) and larger practices (54.5% versus 31.3%). The numbers of principals in medium size practices were well balanced. The 22 practices taking part in this study were located in inner city, suburban and rural areas and served deprived as well as affluent practice populations.

Table 13 Characteristics of practices taking part in the study compared to those in Avon and the UK

	Practices taking part in RCT	**Avon (2001)[a]**	**UK (2001)[b]**
Mean number ± SD of patients per practice	10,285 ± 4461	13,789 (SD not available)	Not available
Mean number ± SD of patients per partner (full-time equivalent)	2132 ± 411	Not available	1,841 (SD not available)
Number of principals by type of practice (%)			
Single-handed	1 (0.9)	Not available	2,900 (8.5)
2 partners	4 (3.6)	Not available	4,122 (12.1)
3 partners	9 (8.2)	Not available	4,716 (13.9)
4 partners	16 (14.5)	Not available	5,844 (17.2)
5 partners	20 (18.2)	Not available	5,675 (17.0)
6 or more partners	60 (54.5)	Not available	10,652 (31.3)

Sources: [a] Avon Practice comparisons, Avon IM&T Consortium 2001 (CD ROM) and [b] Royal College of General Practitioners RCGP Information Sheet No. 2 (Profile of UK practices, available online at http://www.rcgp.org.uk/)

Other characteristics of participating practices

Further characteristics of participating general practices, which are important in terms of the generalisability of this study, are summarised in Table 14. It shows that the number of practice nurses working in the practices (median 3.5) was similar to the number of practice nurses involved in the management of hypertension (median 3). More practices provided teaching (63.6%) in this study than those that did not. All practices used a recall system for managing their hypertensive patients, and 36.4% had a dedicated hypertension clinic.

Although no regional or national data were available for these categories, the study practices appear to provide a reasonably good mix of different practice types and practice populations, although the percentage of teaching practices is likely to be higher than the national average.

Table 14 Characteristics of participating practices

Characteristic	Study practices
Number of nurses managing hypertension, median (range)	3 (1 to 7)
Total number of practice nurses, median (range)	3.5 (1 to 7)
Number of practices (%) receiving Culyer research funding	11 (50)
Number of practices (%) involved in teaching	
Undergraduate only	5 (22.7)
Postgraduate only	1 (4.6)
Both	8 (36.4)
None	8 (36.4)
Type of list, n (%)	
Shared [a]	9 (40.9)
Individual [b]	13 (59.1)
Using a recall system for hypertensive patients [c]	22 (100)
Dedicated hypertension clinic, n (%)	8 (36.4)

[a] 'Shared' means that patients are free to choose any doctor for a consultation, although they may be 'registered' with a particular GP
[b] Patients are registered with a single GP whom they see for most if not all consultations
[c] A system in which patients with high blood pressure are identified, coded and, either by computer or other system, followed up systematically and according to an agreed practice protocol

Characteristics of participating practice nurses

The characteristics of participating practice nurses are summarised in Table 15. The nurses taking part in this study were experienced and well qualified. More than half the nurses were grade F (54.5%), and eight (36.4%) were graded at sister or nurse practitioner level. All nurses had been qualified for a minimum of six years and had worked in their respective general practice for at least two years. All had received training in the management of hypertensive patients, either through in-house training, external courses, or both. All nurses used a standardised protocol that was available in

their consulting room and that had been adapted by the practice from the British Hypertension Society Guidelines for the management of hypertension.[19] It is difficult to know whether the nurses taking part in this study are representative of nurses in the UK, as no national data on the characteristics presented in Table 15 were available to allow a comparison.

Table 15 Characteristics of participating practice nurses

Characteristic	Practice nurses in study
Nursing grade, n (%) [a]	
C	1 (4.6)
E	1 (4.6)
F	12 (54.6)
G	5 (22.7)
H	3 (13.6)
Number of qualifications, median (range)	3 (1 to 4)
Length of time since qualification in years, median (range)	17 (6 to 42)
Length of time working in the practice in years, median (range)	3.5 (2 to 18)
Training in hypertension management, n (%)	
Practice based training only	2 (9.1)
Both internal and external training	20 (90.9)
Using a standardised protocol, n (%)	22 (100)

[a] Nurses in the NHS are graded according to experience. Grades A, B and C are used for health care assistants. The 'D' grade corresponds to a newly qualified staff nurse, and grade E is assigned to more experienced nurses. An F grade is a senior staff nurse and G grade is a charge nurse or sister. Any grade above the G grade usually implies more management responsibilities.

7.2.4 Baseline characteristics of study participants

In this section I summarise the baseline characteristics across the trial arms. All study participants were of Caucasian ethnic origin.

Table 16 describes the baseline demographic and clinical characteristics of both trial groups in terms of the stratifying variables age and sex. The trial groups were comparable for these two variables, although more men than women were eventually taking part in the study (55% versus 45%). Age ranged from 36 to 91 years in the intervention group and from 39 to 87 in the control group.

Table 16 Baseline demographic and clinical characteristics of trial groups in terms of the stratifying variables

Characteristic	Adherence support group (n=128)	Usual care group (n=117)
Mean age (years) ± SD	67.9 ± 10.3 (n=126)	68.2 ± 9.4 (n=116)
Men (%)	56.3 (72/128)	53.9 (63/117)

Mean timing compliance was relatively high and similar for both groups at baseline (Table 17). The distributions for systolic and diastolic blood pressure were very close to our pre-defined cut-off point of 150/90 mmHg and similar in both groups.

Table 17 Baseline clinical characteristics in terms of the main outcome variables timing compliance and blood pressure

Characteristic	Adherence support group (n=128)	Usual care group (n=117)
Mean timing compliance (%) ± SD[a]	90.8 ± 15.6 (n=101)	94.5 ± 7.6 (n=88)
Mean blood pressure at baseline in mmHg) ± SD[b]		
Systolic	149.0 ± 15.2 (n=127)	152.1 ± 17.5 (n=114)
Diastolic	83.7 ± 9.3 (n=127)	83.1 ± 9.9 (n=114)

[a] Measured over one month baseline period
[b] This is the mean of the blood pressures at the beginning and the end of the one month baseline observation period prior to administration of the intervention.

Figure 16 shows the frequency distribution of timing compliance for all study participants. As expected, the distribution was skewed to the left. As can be seen from Figure 17 and Figure 18, there were no major differences in the frequency distributions

of timing compliance in both intervention groups. The majority of participants showed high timing compliance.

Figure 16 Frequency distribution of timing compliance (%) at baseline for all participants

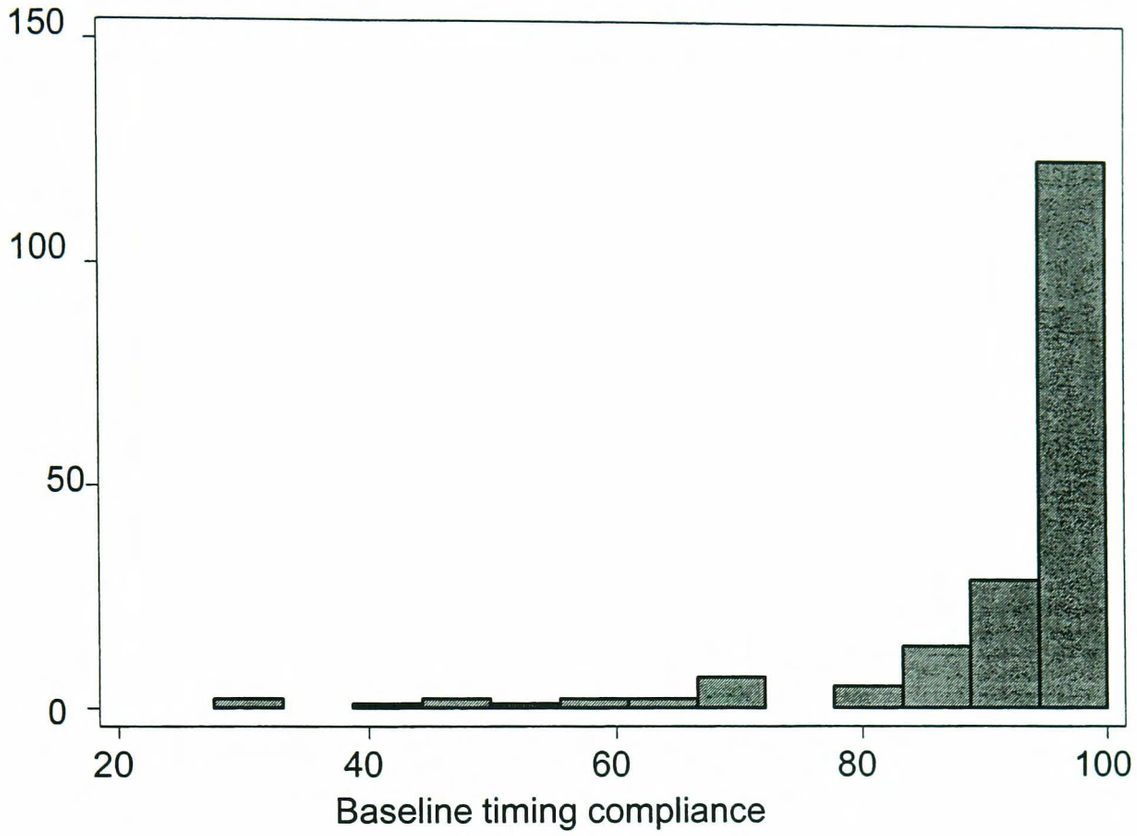


Figure 17 Frequency distribution of timing compliance (%) at baseline in the control group

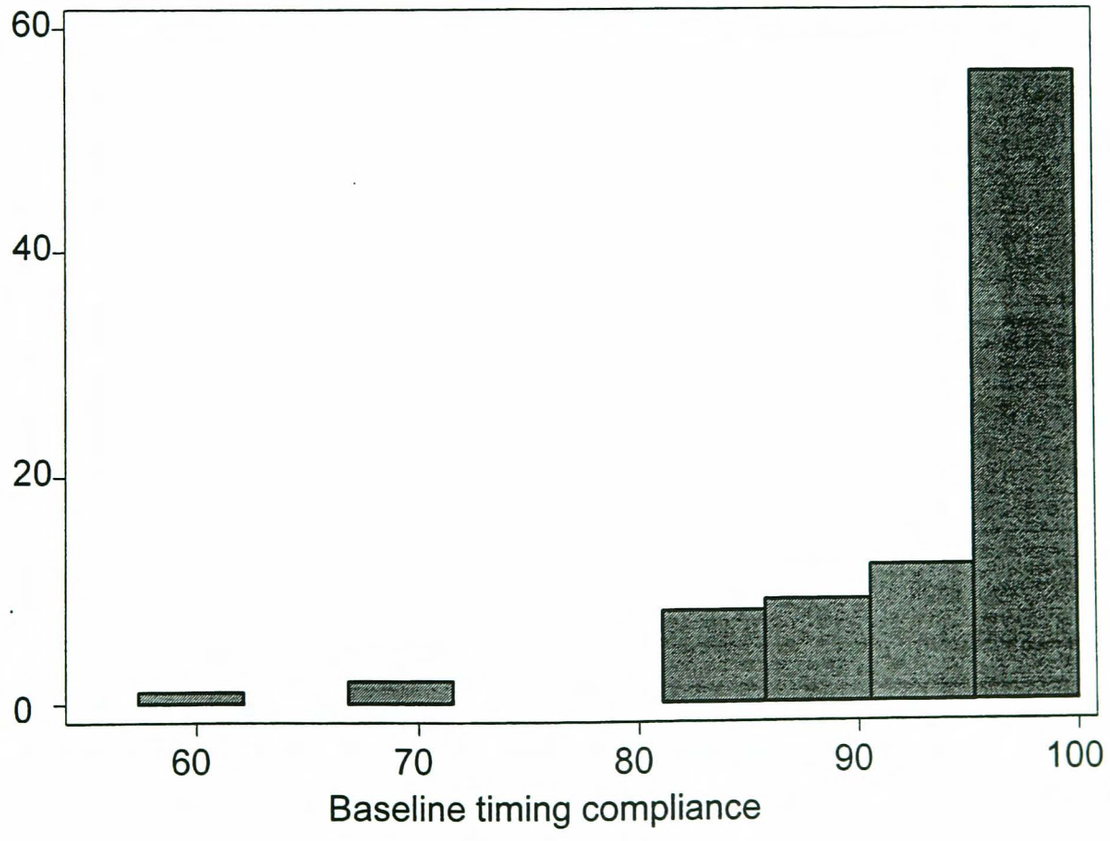


Figure 18 Frequency distribution of timing compliance at baseline in the intervention group

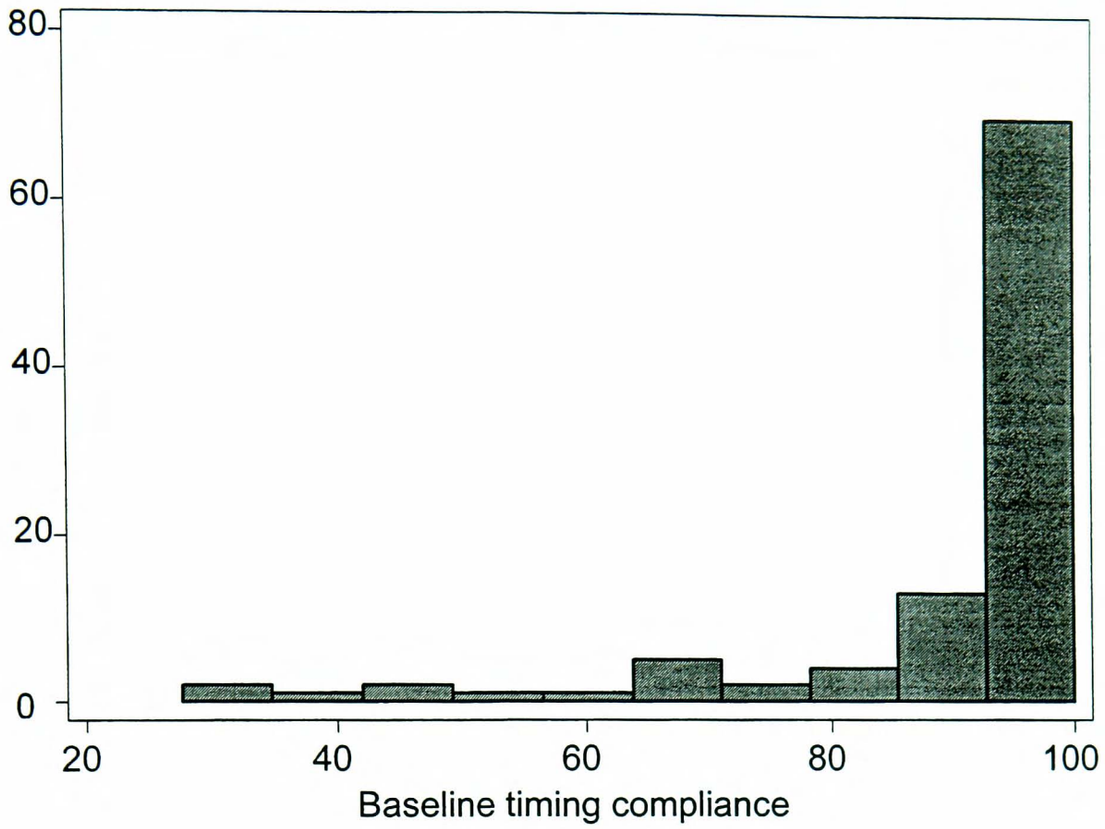


Figure 19 and Figure 20 show the frequencye distributions for the secondary outcome blood pressure. As expected, both systolic and diastolic blood pressure were normally distributed in the study participants.

Figure 19 Frequency distribution of baseline systolic blood pressure for all participants

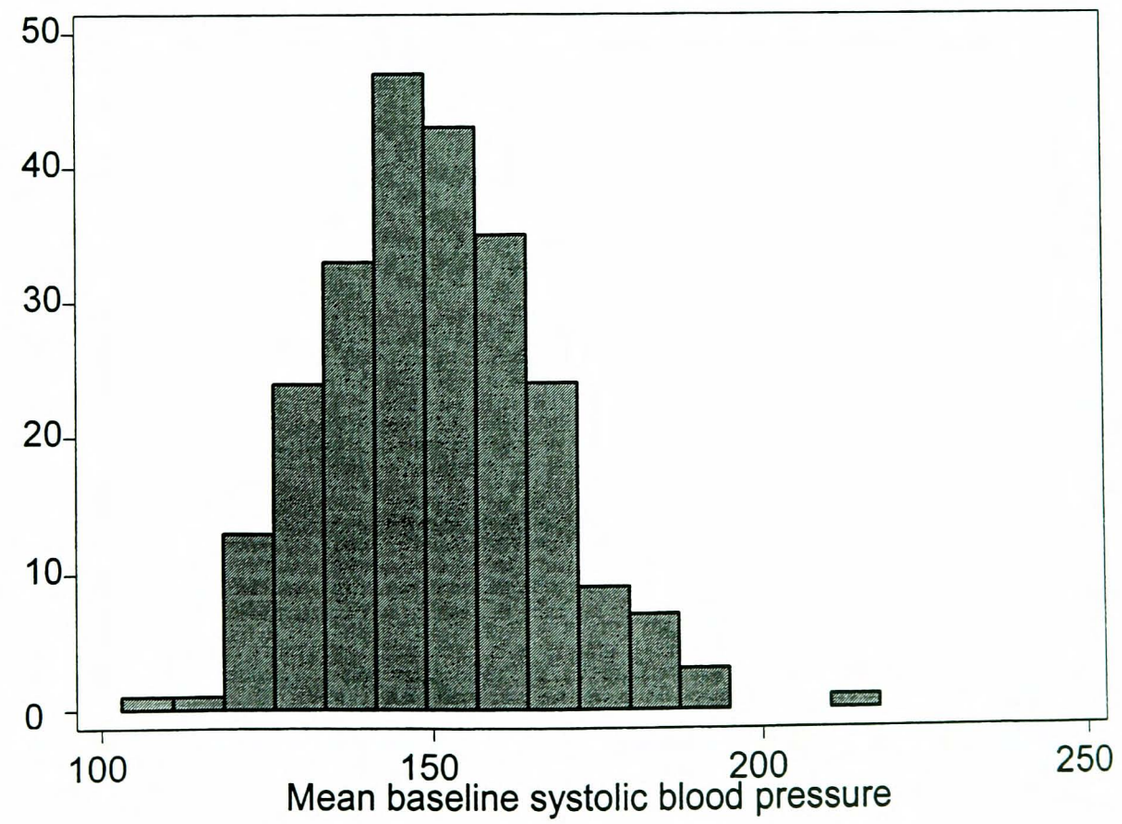


Figure 20 Frequency distribution of baseline diastolic blood pressure for all participants

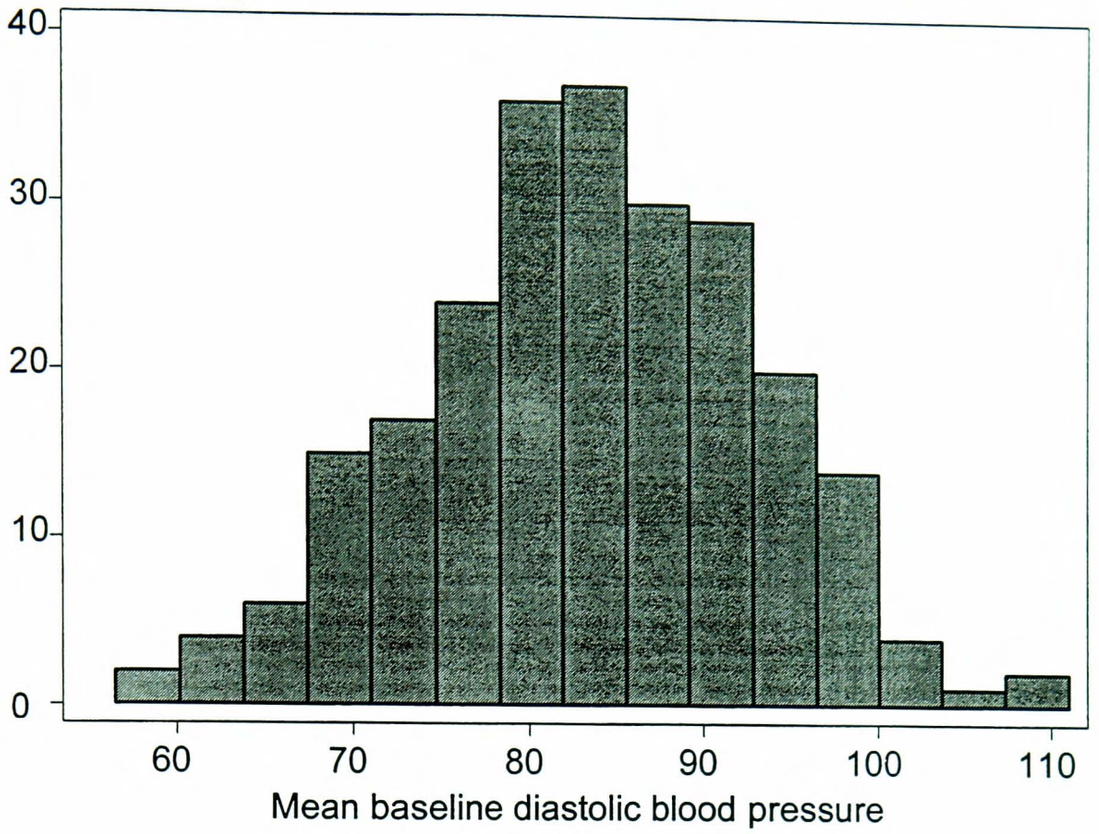


Table 18 compares the means of the adherence variables 'correct dosing' and 'taking compliance' for the intervention and control groups. Adherence was well balanced between the two groups when using these less strict measures of adherence. As expected, adherence was higher in both groups compared to the stricter measure of 'timing compliance'.

Table 18 Baseline adherence in terms of 'correct dosing' and 'taking compliance'

Characteristic	Adherence support group (n=128)	Usual care group (n=117)
Correct dosing (% of days on which the correct number of doses was taken) ± SD	95.6 ± 9.5 (n=101)	97.6 ± 4.4 (n=88)
Taking compliance (% of prescribed number of doses taken) ± SD	98.6 ± 7.3 (n=101)	99.4 ± 3.8 (n=88)

Information about the distribution of important cardiovascular risk factors in both groups is provided in Table 19. The distributions of smoking status, body mass index, cholesterol, family history of hypertension, and a diagnosis of diabetes mellitus are very similar. There was a 4.7% difference between the study groups with regard to a past

history of cardiovascular disease (that is, a diagnosis on the practice register of stroke, angina, or myocardial infarction).

Table 19 Baseline characteristics in terms of important cardiovascular risk factors

Characteristic	Adherence support group (n=128)	Usual care group (n=117)
Smokers (%)	10.0 (13/128)	9.4 (11/117)
Mean body mass index (BMI, kg/m2) ± SD	29.1 ± 5.2 (n=118)	29.3 ± 5.2 (n=106)
Mean cholesterol (mmol/l) ± SD[a]	5.3 ± 1.3 (n=99)	5.4 ± 1.2 (n=82)
Family history of hypertension (%)	48.4 (60/124)	50.9 (59/116)
Diabetes mellitus (%)	17.1 (21/123)	16.2 (19/117)
Past history of cardiovascular disease (%)	36.6 (45/123)	31.9 (37/116)

[a] 'Latest' blood samples, taken between 4 November 1987 and 18 January 2002

The characteristics of the trial participants in each randomisation group with respect to their medication usage are presented in Table 20 and Table 21. For the number of blood pressure tablets per dose and the total number of oral drugs, the distributions between trial groups were similar. However, there were differences between intervention and control groups for most other variables. About 8% more participants in the intervention group used over the counter medicines (55.7% versus 47.4%). The proportion of patients on twice daily regimen for the tablet dispensed by the electronic monitor was also higher in the intervention group (4.8% versus 1.8%). The drug group used in the electronic monitor was less likely to be a diuretic (47.2% versus 53.9%) or a calcium antagonist (11.0% versus 17.4%) in the intervention arm and more likely to be an ACE inhibitor (13.4% versus 6.1%).

Table 20 Baseline characteristics in relation to medication usage

Characteristic	Adherence support group (n=128)	Usual care group (n=117)
Additional use of over the counter medicines (%)[a]	55.7 (68/122)	47.4 (55/116)
Drug group dispensed from the electronic monitor (%)		
Diuretic	47.2 (60/127)	53.9 (62/115)
Beta blocker	21.3 (27/127)	18.3 (21/115)
Calcium antagonist	11.0 (14/127)	17.4 (20/115)
ACE inhibitor	13.4 (17/127)	6.1 (7/115)
Other	7.1 (9/127)	4.4 (5/115)
Doses dispensed from the electronic monitor per day, (%)		
Once daily	94.4 (118/125)	98.2 (107/109)
Twice daily	4.8 (6/125)	1.8 (2/109)
Three times daily	0.8 (1/125)	0 (0/109)
Number of blood pressure tablets per dose dispensed from the electronic monitor (%)		
One	98.4 (123/125)	100 (109/109)
Two	1.6 (2/125)	0 (0/109)
Total number of oral drug prescriptions (%)		
1 to 2	21.6 (19/88)	20.3 (15/74)
3 to 5	54.6 (48/88)	58.1 (43/74)
6 or more	23.9 (21/88)	21.6 (16/74)

Most trial participants had been on blood pressure lowering medication for a number of years. The proportions of participants with a duration of blood pressure treatment of one year or less was similar between groups (Table 21). A higher percentage of participants in the intervention group were on treatment for between one and five years (39.1%

versus 27.4%). The control group had a higher percentage of participants who had been on blood pressure treatment for more than five years (65.0% versus 50.8%). There were also more participants in the control group who had a blood pressure change in the preceding 12 months due to poor blood pressure control (57.9% versus 43.3%).

Table 21 Baseline characteristics in relation to treatment duration and changes in blood pressure lowering medication

Characteristic	Adherence support group (n=128)	Usual care group (n=117)
Duration of blood pressure treatment (%)		
< 6 months	2.3 (3/128)	2.6 (3/117)
6 to 12 months	6.3 (8/128)	5.1 (6/117)
> 1 year to 5 years	39.1 (50/128)	27.4 (32/117)
> 5 years	52.3 (67/128)	65.0 (76/117)
Change in blood pressure medication in past 12 months (%)	46.7 (57/122)	42.0 (47/112)
Reason for change in blood pressure medication (%)		
Side effects	19.4 (13/67)	17.5 (10/57)
Poor control	43.3 (29/67)	57.9 (33/57)
Both	14.9 (10/67)	7.0 (4/57)
Other	7.5 (5/67)	0 (0/57)

Summary

The general practices and participants recruited to the trial appear to be broadly representative in terms of external validity. The study groups did generally not show major differences in terms of basic baseline characteristics, indicating a successful randomisation procedure. However, for some variables, in particular the characteristics of drug use, there were some differences between the groups, which were further investigated in secondary analyses (see section 7.5 below).

7.3 Process measures in the intervention and control groups between recruitment and follow-up at six months

This RCT was complex in terms of its various stages from baseline to final follow-up as well as in terms of its intervention. This section presents data of process measures that were observed as part of the follow-up of study participants and the delivery of the intervention. Where differences were observed between the different groups, the effects of these process measures on the relationship between explanatory variables and the outcomes of interest are presented in Section 7.5.2.

7.3.1 Non-attendance at follow-up

Participants attended their baseline appointments between 28 January 2001 and 27 May 2002. The appointments for delivery of the intervention took place between 2 January 2001 and 26 March 2002. The follow-up at two months occurred between 7 February 2001 and 16 August 2002, and the final follow-up at six months took place between 12 April 2002 and 11 December 2002.

As shown in the CONSORT flow diagram (Figure 15), the numbers of participants who were not followed up were similar in the intervention and control groups. Moreover, there were on the whole no major differences in losses to follow-up between the groups when analysed within the strata of the pre-determined stratifying variables age and sex.

Table 22 presents the results for the numbers of men and women lost to follow-up in both comparison groups at each stage of the trial. Losses to follow-up were reasonably well balanced between the groups in terms of sex apart from a higher percentage of women at six month in the usual care group (10.2% versus 3.9%). However, this difference was not statistically significant ($p = 0.39$).

Table 22 Losses to follow-up in % (number/total) in both comparison groups by sex

	Adherence support group (n=128)		Usual care (n=117)		
	Men	Women	Men	Women	p-value
Two month follow-up	3.9 (5/128)	2.3 (3/128)	2.5 (3/117)	1.7 (2/117)	0.92 [a]
Six month follow-up	3.9 (5/128)	3.9 (5/128)	5.1 (6/117)	10.2 (12/117)	0.39 [b]

[a] $\chi^2 = 0.008$, df=1 [b] $\chi^2 = 0.75$, df = 1

Table 23 presents the results for the number of participants by age group who were lost to follow-up in both comparison groups at two and six months after randomisation. Losses to follow-up for the over 60s age group were slightly higher in the intervention group compared to controls (5.5% versus 3.4%). At six months, the differences in this age group were reversed, and losses to follow-up were higher in the usual care group (13.6% versus 5.5%). Both differences were, however, not statistically significant.

Table 23 Losses to follow-up in % (number/total) in both comparison groups by age group

	Adherence support group (n=128)		Usual care (n=117)		
	<60	60 and over	<60	60 and over	p-value
Two month follow-up	0.8 (1/128)	5.5 (7/128)	0.9 (1/117)	3.4 (4/117)	0.72 [a]
Six month follow-up	2.3 (3/128)	5.5 (7/128)	1.7 (2/117)	13.6 (16/117)	0.21 [b]

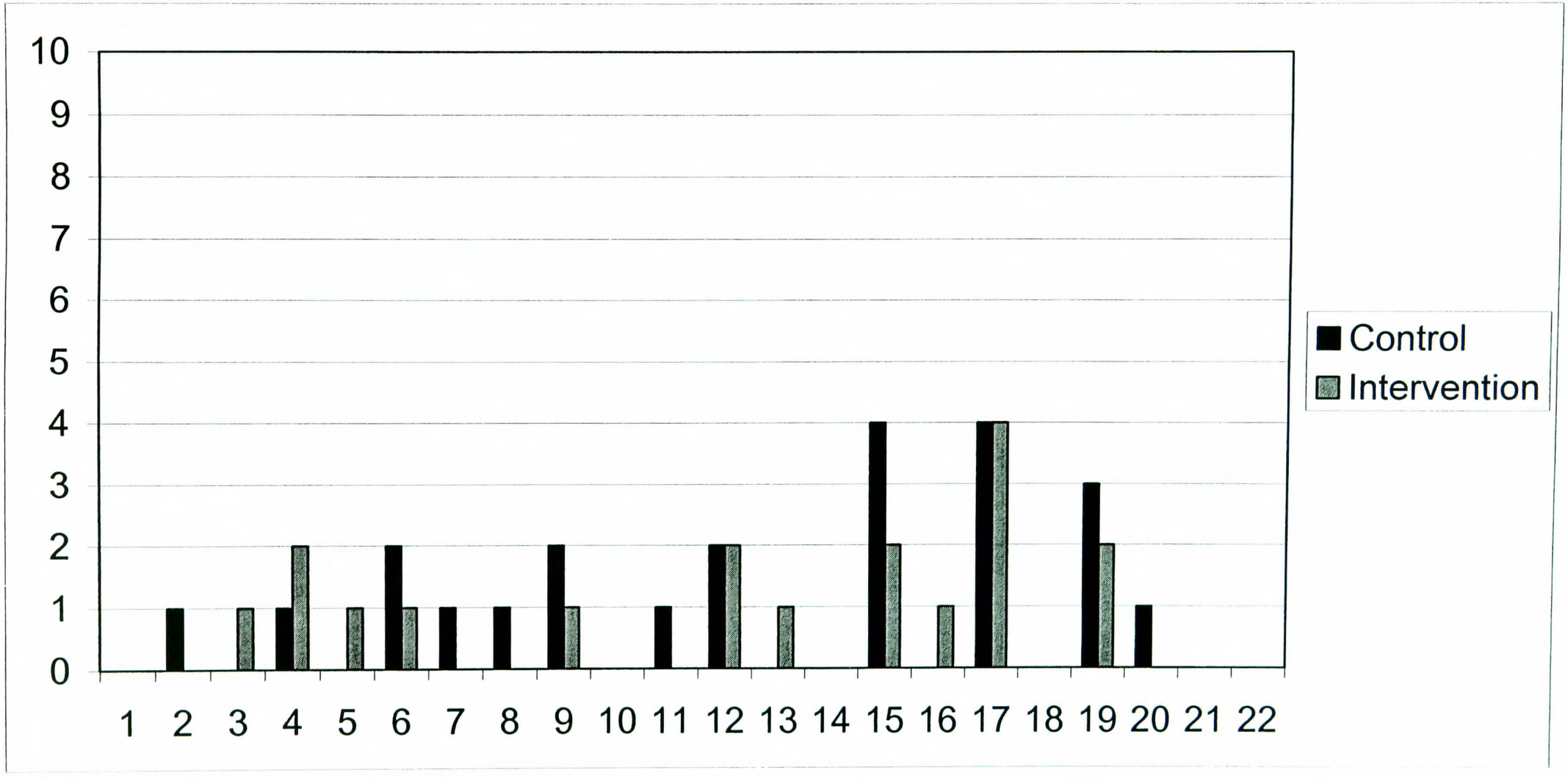
[a] $\chi^2 = 0.13$, df=1 [b] $\chi^2 = 1.56$, df = 1

Figure 21 shows the total number of losses to follow-up in the intervention and control groups at six months for each practice. A total of 41 out of the 245 patients randomised (16.7%) were lost to follow-up, with generally small numbers of follow-up occurring in 16 practices. Five of the practices for which patients were randomised did not have any losses to follow-up, and the maximum number of losses to follow-up in a single practice was eight.

One practice withdrew entirely from the study because the practice nurse fell ill after participants had been recruited but before they were invited for the initial appointment

(Practice 22). Another practice had a total loss to follow-up of 8 participants at the two month follow-up, because the practice nurse had resigned without handing over responsibility for following up the trial participants (Practice 17). Six losses to follow-up in Practice 15 were due to sudden long-term illness of the practice nurse responsible for running the study in that centre.

Figure 21 Total number of losses to follow-up at six months by practice



In summary, there were no important statistically significant differences between the intervention and control groups in terms of age or sex in terms of differential losses to follow-up. However, there were differences in losses to follow-up between practices, the main reason being that practice nurses were leaving or falling sick.

7.3.2 Process measures in the intervention group

The intervention evaluated in this trial consisted of a nurse-led adherence support intervention, lasting about 20 minutes, and a reinforcement follow-up appointment two months later (Figure 10).

First adherence support consultation

The intended length of the appointment for delivering the intervention was 20 minutes, and all practice nurses booked appointments for study participant at these intervals. Although the nurses did not record the exact timing of each appointment, based on verbal feedback they all found this time adequate to deliver the intervention. None of the practice nurses routinely asked detailed questions about medication adherence before taking part in this trial, although two of them reported that they occasionally, but not in a structured way, asked whether patients had any problems with their medication.

This section presents results on how consistently the practice nurses delivered the intervention. The practice nurses were given a data collection sheet (see Appendix 5) and were asked to complete a log of the topics they discussed with their patients during the adherence support intervention. This process included an introduction aiming to put patients at ease and outlining the reason for the appointment. The next question aimed to provide the basis for a discussion about any problems that patients had with taking their medicines.

Table 24 presents the number of nurses who recorded that they have addressed these questions or statements with their patients. The nurses reported having covered these topics at the start of the consultation in more than 80% of participants. Investigating this at practice level, eight out of the 21 practice nurses delivering the intervention (38.0%) reported covering these questions in all their patients, and one practice nurse did not tick these questions for any of her patients. The mean percentage of missing data for the remaining 12 practices was 63.1% (SD 20.2, range 12.5 to 80), which indicates varying recording habits from practice to practice.

Table 24 Process measures in relation to the introductory questions during the adherence support intervention

Questions/statements by the practice nurses when delivering the intervention	**Discussed during adherence support intervention (n=128)**
Introduction statement made: "Please state that many people find it difficult to take their medication all the time" (%)	85.2 (109/128)
Explained that "...the reason for the appointment is to discuss ANY problems with taking blood pressure tablets" (%)	82.0 (105/128)

The next process measure of interest in the intervention group was the extent to which the nurses addressed single problems with medication (Appendix 5). In 103 participants (85.8%) did the nurses cover all potential problems with their patients' medication. However, in 12 participants (9.4%) did the practice nurses not record coverage of individual barriers at all.

Medication problems in the intervention group

A major component of the intervention was structured questioning about any problems with medication taking, that is, barriers to medication adherence. The findings with regard to problems with medication taking in the intervention group are presented in Table 25. Only about one quarter of participants reported having a problem with their medication, with the most common problem being side effects (14.1%) followed by forgetfulness (10.9%).

Table 25 Numbers of participants who admitted to problems with medication taking in the intervention group

Problem	Per cent of intervention group
Participants who admitted having problems with their medication (%)	24.2 (31/128)
Total number of problems (%)	
0	72.3 (81/112)
1	18.8 (21/112)
2	7.1 (8/112)
3	1.8 (2/112)
Missing	12.5 (16/128)
Side effects (%)	14.1 (18/128)
Size or taste of tablets (%)	2.3 (3/128)
Number of doses per day (%)	0 (0/128)
Acceptability of blood pressure treatment (%)	1.6 (2/128)
Forgetfulness (%)	10.9 (14/128)
Comprehension (%)	2.3(3/128)
Total number of tablets (%)	1.6 (2/128)

Process measures in the intervention group with respect to the strategies that were agreed to resolve medication problems

An important part of the intervention was for patient and practice nurse to agree a strategy to address any problems with medication taking. Table 26 presents information on the numbers of participants in the intervention group in whom nurses and patients agreed a strategy to address medication problems, if these were present. In five categories of barriers to medication adherence, namely (1) the size or taste of tablets, (2) acceptability of blood pressure treatment, (3) forgetfulness, (4) comprehension of what high blood pressure is, and (5) the total number of tablets per day, the nurses and patients agreed strategies in all cases. Figures for side effects (72.2%) were lower. Reasons for this were that participants did not want to see their GP (3 participants) or had already discussed this with the GP and decided to put up with the side effects (2 participants). The strategies adopted for reducing side effects and dealing with an

unpleasant size or taste of the tablets consisted of referrals back to the GP in all cases. To reduce forgetfulness, nurses and patients mainly introduced tailoring of medication taking to daily habits (12 participants) and family support, that is, reminders by the partner at home, in two participants.

Table 26 Percentages of participants in the intervention group in whom a strategy to address problems with medication taking was agreed

Problem in the intervention group	Per cent of participants presenting with this problem	Participants in whom strategy was agreed
Side effects (%)	10.2 (13/128)	72.2 (13/18)
Size or taste of tablets (%)	2.3 (3/128)	100 (3/3)
Number of doses per day (%)	0 (0/128)	n/a (0)
Acceptability of blood pressure treatment (%)	1.6 (2/128)	100 (2/2)
Forgetfulness (%)	10.9 (14/128)	100 (14/14)
Comprehension (%)	2.3 (3/128)	100 (3/3)
Total number of tablets (%)	1.6 (2/128)	100 (2/2)

Process measures in the intervention group with respect to the success of the strategies used to address medication problems

Table 27 presents information about the success of the strategies adopted for the individual medication problems that study participants presented with. Amongst participants who agreed a strategy to address the size or taste of tablets, the acceptability of blood pressure treatment, or comprehension or the total number of tablets, all (100%) of the participants stated that the strategy used had been successful and that the problem had ceased to exist. The percentages for forgetfulness (92.9%) and side effects (76.9%) were slightly lower, with missing values (forgetfulness) and reluctance to make an appointment with the GP (side effects) being the main reasons.

Table 27 Numbers of participants in the intervention group in whom the strategy to address problems with medication taking was successful

Problem in the intervention group	Per cent of participants in whom this problem was addressed	Per cent of participants in whom the strategy was successful
Side effects (%)	7.8 (10/128)	76.9 (10/13)
Size or taste of tablets (%)	2.3 (3/128)	100 (3/3)
Number of doses per day (%)	0 (0/128)	n/a (0)
Acceptability of blood pressure treatment (%)	1.6 (2/128)	100 (2/2)
Forgetfulness (%)	10.2 (13/128)	92.9 (13/14)
Comprehension (%)	2.3 (3/128)	100 (3/3)
Total number of tablets (%)	1.6 (2/128)	100 (2/2)

7.3.3 Appointments for the control group and potential for contamination

The appointment for the control group consisted of simple blood pressure checks and downloading of the electronic monitors, which took place at the same intervals as the follow-up appointments in the intervention group. The length of these appointments varied from five to 10 minutes, according to local usual practice. In the majority of practices, another nurse who was not involved in delivering the intervention conducted the follow-up in the control group. In four practices, however, the same nurses followed up both groups. All these nurses reported that they only delivered their 'usual care' to the control group and that they did not start to talk about medication adherence, unless this was something they would normally do.

7.4 Primary analysis of outcomes

7.4.1 Comparison of medication adherence between the intervention and control participants (primary outcome)

As discussed in Chapter 5, the primary outcome determined *a priori* was adherence to medication, defined as 'timing compliance', which is the percentage of a prescribed number of doses taken in a specified correct interval. This measure is the 'strictest'

compared to other measures of adherence such as 'taking compliance' or 'pill counts'. For the primary intention-to-treat analysis, data from the electronic monitors were available for 160 participants, with 85 out of 128 randomised participants (66.4%) in the intervention group and 75 (64.1%) in the control group.

Figure 22 shows a histogram of timing compliance with a superimposed normal distribution. This is an informal way of looking at the distribution of timing compliance. Although the histogram is skewed to the left, it appears to be close enough to the normal distribution to allow the data to be used for regression analysis without further transformation given the reasonably large sample size.

Figure 22 Frequency distrubution of timing compliance over the six months follow up with superimposed normal distribution

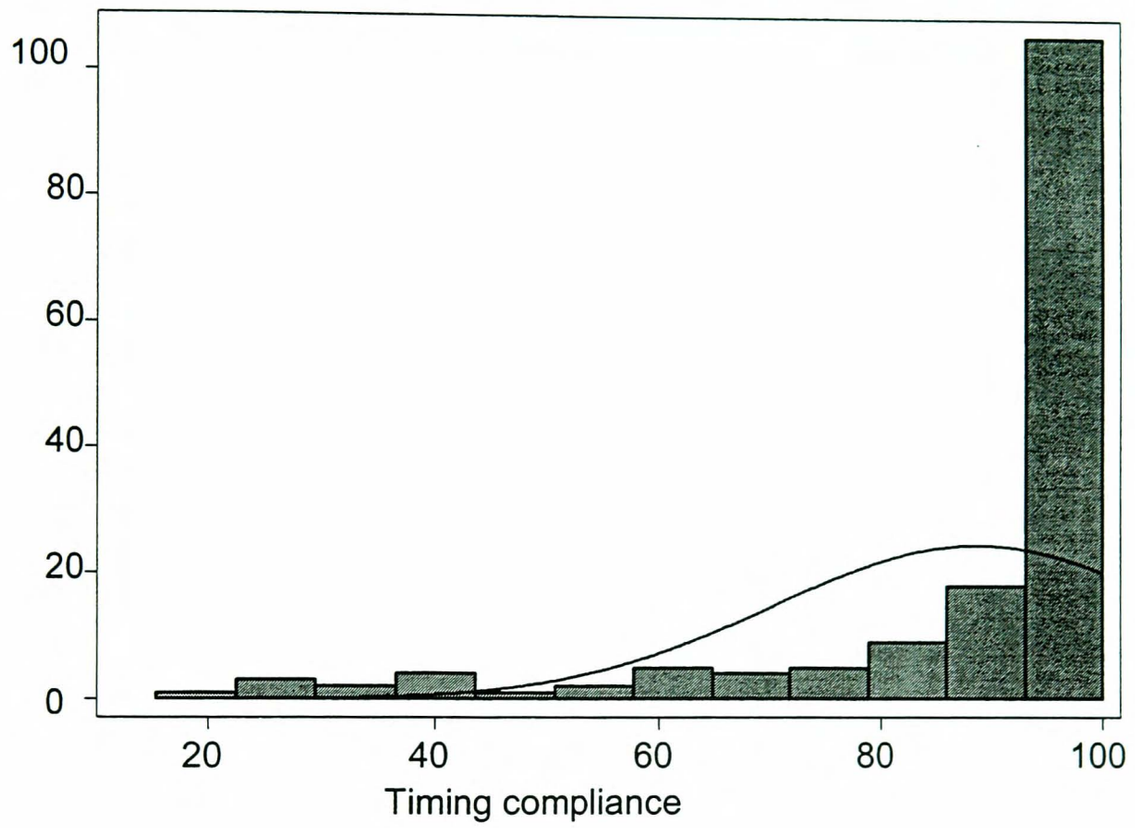


Table 28 presents results from the regression model, comparing adherence between the intervention and control groups in the six months period following the intervention. There were no overall differences in timing compliance between the intervention and control groups (adjusted difference between means of timing compliance: -1.0%, 95% CI -5.1 to 3.1, p=0.63). Similarly, for 'correct dosing' and 'taking compliance' there were also no important differences between the groups. Adherence was generally high in both comparison groups for the three definitions of adherence. As expected, mean adherence was higher if less strict definitions of adherence were applied.

Table 28 Regression model comparing adherence between intervention and control groups in the six months period following the intervention, controlling for baseline measurement of adherence and stratifying variables (general practice, age group and sex)

	Nurse-led adherence support (AS)	**Usual care (UC)**	**Adjusted difference (AS-UC)[a] between means (95% CI)**	**p-value**
Timing compliance (% of days in which the correct number of doses were taken on time), mean (SD), n=159	87.2 (20.1)	90.2 (16.2)	-1.0 (-5.1 to 3.1)	0.63
Correct dosing (% of days on which the correct number of doses was taken), mean (SD), n=159	90.8 (16.6)	92.4 (15.2)	-0.5 (-4.2 to 3.1)	0.77
Taking compliance (% prescribed number of doses taken), mean (SD), n=159	95.6 (16.4)	95.6 (15.7)	-0.6 (-3.2 to 4.4)	0.76

[a]A *positive* difference indicates an *increase* in adherence for AS compared with UC

7.4.2 Comparison of blood pressure between the intervention and control participants (secondary outcome)

The following two figures show histograms for the secondary outcomes systolic and diastolic blood pressure at the six month follow-up. Not surprisingly, these are close to the normal distribution, allowing regression analysis without further transformation of the data.

Figure 23 Frequency distribution of systolic blood pressure at 6 month follow-up with superimposed normal distribution

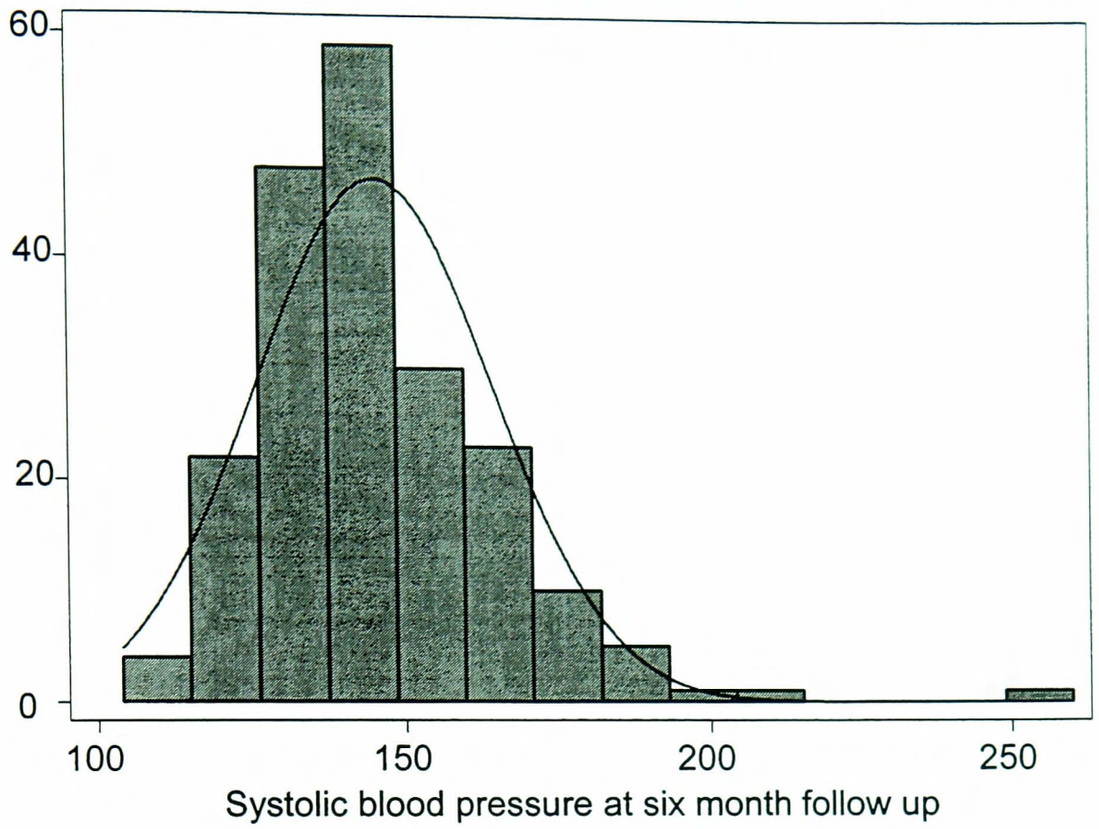


Figure 24 Frequency distribution of diastolic blood pressure at six month follow-up with superimposed normal distribution

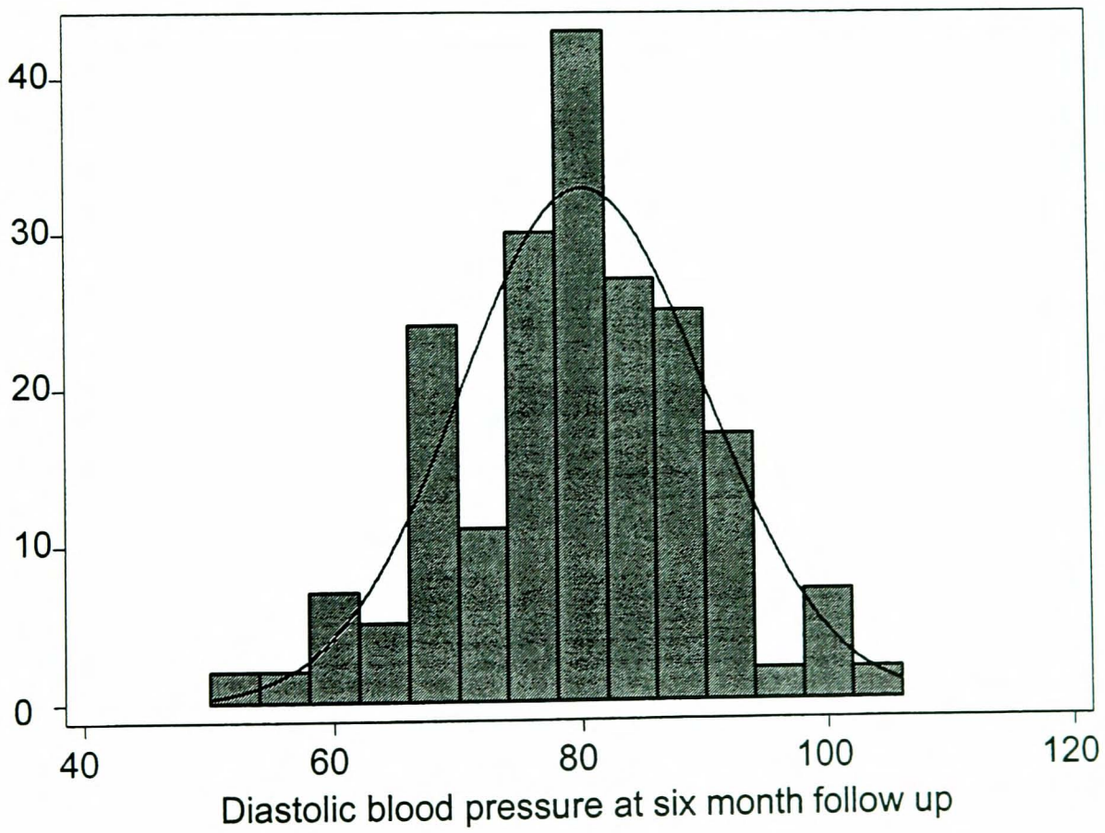


Table 29 presents results from a regression model comparing blood pressure between the intervention and control groups at six months. There was also no difference between

the intervention and control groups at the six months follow-up in terms of systolic (adjusted difference between means -2.7mmHg, 95% CI: -7.2 to 1.8, p=0.24) or diastolic blood pressure (adjusted difference between means (mmHg): 0.2, 95% CI: -1.9 to 2.3, p=0.85).

Table 29 Regression model comparing mean blood pressure between the intervention and control groups at six months, controlling for baseline measurement of blood pressure and stratifying variables (general practice, age group and sex)

	Nurse-led adherence support (AS), mean (SD)	**Usual care (UC), mean (SD)**	**Adjusted difference (AS-UC) between means (95% CI)[a]**	**p-value**
Systolic blood pressure (mmHg), n=200	142.9 (17.6)	147.7 (20.9)	-2.7 (-7.2 to 1.8)	0.24
Diastolic blood pressure (mmHg), n=200	80.4 (10.1)	79.9 (9.7)	0.2 (-1.9 to 2.3)	0.85

[a] A *negative* difference (AS-UC) indicates a *reduction* in blood pressure

7.4.3 Missing values

The number of missing values for the main outcomes at six months was relatively high and amounted to n=85 (43 intervention and 42 control) for timing compliance and n=41 (18 intervention and 23 control) for systolic as well as diastolic blood pressure. The following tables present the results of the regression models for the effect of the intervention on timing compliance and adherence, comparing the ITT model with a model where any missing values were replaced with the last observation from the two month follow-up. If this was also missing, the baseline observation was carried forward. This model assumes that the observations did not change and therefore may provide a conservative estimate. As shown in the tables, replacing the missing values with the last observation carried forward did not lead to any important changes in the results.

Table 30 Results of the regression model for the effect of the intervention on timing compliance at six month, replacing missing values with the last observation carried forward

	Difference between means (%)	95% CI	p-value
ITT	-1.0	-5.1 to 3.1	0.63
Last observation carried forward	1.5	-1.8 to 4.7	0.38

Table 31 Results of the regression model for the effect of the intervention on systolic blood pressure at six month, replacing missing values with the last observation carried forward

	Difference between means (mmHg)	95% CI	p-value
ITT	-2.7	-7.2 to 1.8	0.24
Last observation carried forward	-0.9	-4.7 to 2.8	0.64

Table 32 Results of the regression model for the effect of the intervention on diastolic blood pressure at six month, replacing missing values with the last observation carried forward

	Difference between means (mmHg)	95% CI	p-value
ITT	0.2	-1.9 to 2.3	0.85
Last observation carried forward	1.3	-0.8 to 3.5	0.22

7.5 Secondary analyses

The secondary analyses comprised first additional adjustment in the regression models in terms of any potentially influential variables that exhibited possible imbalance at baseline. Secondly, pre-planned subgroup analyses for age, sex, drug group and total number of drugs prescribed were conducted by introducing appropriate interaction terms to investigate differential effects.

7.5.1 Additional adjustment for variables that showed imbalance at baseline

Seven variables showed at least some degree of imbalance at baseline between the intervention and control groups. In order to exclude a potential effect of even a minor imbalance on the main study outcomes, it was decided to conduct additional adjustment for these variables. In this section will report the results of the comparison between intervention and control groups, adjusting for these variables.

Adherence

Table 33 presents the results of the regression model for timing compliance at six months, adjusting for additional variables that showed some potential imbalance at baseline. Adding these variables to the basic model did not lead to any important changes in the results. The difference in timing compliance between groups increased to 5.6% in favour of the intervention when adding reasons for changing blood pressure medication to the model, but the confidence intervals were wide and the difference not statistically significant, which is likely due to the relatively large number of missing values. Residuals from the models were examined graphically for normality through a histogram and normal plot. For all models, the residuals were distributed relatively close to the normal distribution (data not shown).

Table 33 Results of a regression model for the effect of the intervention on timing compliance at six month after additional adjustment for variables that showed imbalance at baseline between the groups

Additional factors adjusted for	Difference between means (%)	95% CI (%)	p-value
'ITT' model (n=159)	-1.0	-5.1 to 3.1	0.63
History of cardiovascular disease (n=155)	-1.1	-5.3 to 3.2	0.62
Use of over the counter medicines (n=153)	-0.9	-5.2 to 3.4	0.68
Total number of doses per day (n=155)	-0.9	-5.2 to 3.4	0.68
Drug group used in electronic monitor (n=159)	-1.2	-5.3 to 2.9	0.57
Duration of blood pressure treatment (n=159)	-1.3	-5.6 to 2.9	0.53
Change in blood pressure medication in past 12 months (n=153)	-1.2	-5.3 to 3.0	0.58
Reason for changing blood pressure treatment in past 12 months (n=71)	5.7	-1.2 to 12.3	0.10
Self assessment of adherence (n=154)	0.8	-3.1 to 4.7	0.69

Systolic blood pressure

Table 34 and Table 35 present the results for the difference between the means for systolic and diastolic blood pressure with confidence intervals and p-values, after adjusting for variables that showed an imbalance at baseline. Adjusting for these variables did not substantially alter the basic model. As for the adherence data, the residuals were normally distributed (data not shown).

Table 34 Results of a regression model for the effect of the intervention on systolic blood pressure at six months after additional adjustment for variables that showed imbalance at baseline between the groups

Systolic blood pressure: Additional factors adjusted for individually	**Difference between means (mmHg)**	**95% CI (mmHg)**	**p-value**
'ITT' model (n=200, see Table 29)	-2.7	-7.2 to 1.8	0.24
History of cardiovascular disease (n=196)	-2.7	7.3 to 1.9	0.25
Use of over the counter medicines (n=194)	-2.5	-7.1 to 2.1	0.28
Total number of doses per day (n=193)	-3.3	-8.0 to 1.4	0.16
Drug group used in electronic monitor (n=200)	-2.7	-7.3 to 1.9	0.24
Duration of blood pressure treatment (n=200)	-2.8	-7.3 to 1.8	0.23
Change in blood pressure medication in past 12 months (n=193)	-2.6	-7.2 to 1.9	0.25
Reason for changing blood pressure treatment in past 12 months (n=101)	-2.1	-9.3 to 5.1	0.57
Self assessment of adherence (n=194)	-2.8	-7.3 to 1.7	0.22

Table 35 Results of a regression model for the effect of the intervention on diastolic blood pressure at six months after adjusting for variables that showed imbalance at baseline between the groups

Diastolic blood pressure: Additional factors adjusted for	**Difference between means (mmHg)**	**95% CI (mmHg)**	**p-value**
'ITT' model (see Table 29) (n=200)	0.2	-1.9 to 2.3	0.85
History of cardiovascular disease (n=196)	0.2	-1.9 to 2.4	0.83
Use of over the counter medicines (n=194)	0.2	-1.9 to 2.4	0.84
Total number of doses per day (n=193)	0.4	-1.9 to 2.6	0.76
Drug group used in electronic monitor (n=200)	0.4	-2.1 to 2.2	0.97
Duration of blood pressure treatment (n=200)	0.1	-2.1 to 2.3	0.92
Change in blood pressure medication in past 12 months (n=193)	0.4	-1.7 to 2.5	0.74
Reason for changing blood pressure treatment in past 12 months (n=101)	1.26	-2.3 to 4.8	0.48
Self assessment of adherence (n=194)	0.3	-1.8 to 2.5	0.76

7.5.2 Secondary explanatory analyses with additional adjustment for process variables

This RCT was designed as a pragmatic trial, and all the analyses described above were carried out on what was essentially an intention-to-treat basis. Since the intervention evaluated in this study was complex, it is important to investigate whether process measures may have influenced any effects of the intervention on the main outcomes.

In this section, I present the results of secondary analyses for the primary and secondary outcomes. These analyses therefore take an explanatory approach and move away from being primarily pragmatic.

Time between appointments

As outlined in Chapter 5, the trial schedule consisted of an initial visit for distribution of the electronic monitors, allowing baseline measurement of adherence prior to the intervention. This was followed by the appointment for the main intervention and further follow-up at two and six months. In this section I consider whether there are any differences between the comparison groups in terms of the time between these appointments, which could have altered an effect of the intervention according to the length of these periods.

Table 36 presents descriptive results for the length of follow-up in both comparison groups in terms of days between practice visits. The means for the length of follow-up for the three periods were close to the desired intervals as stated in the protocol and even slightly longer for the baseline period.

Table 36 Comparison between the intervention and control groups in terms of time between appointments

Time between appointments	Nurse-led adherence support	Usual care	Total
Baseline (initial appointment to date of intervention) in days, mean (SD)	38.7 (15.6)	37.1 (17.7)	38.0 (16.6)
Two month following the intervention in days, mean (SD)	64.4 (18.9)	64.3 (18.0)	64.4 (18.4)
Six months following the intervention in days, mean (SD)	183.2 (27.4)	184.0 (33.5)	183.6 (30.2)

Table 37 shows the estimates for the differences in means and 95% confidence intervals between the groups for the time between practice visits. These differences were small and not statistically significant, indicating that the practice nurses were successful in adhering to the study protocol for both comparison groups.

Adjusting for the time between visits made essentially no difference to the results for adherence, systolic and diastolic blood pressure (results presented in Table 38, Table 39 and Table 40).

Table 37 Estimates and 95% confidence intervals (CI) for the difference (Control minus Intervention) in mean time between practice visits

	Difference (usual care minus intervention)	**95% CI**	**p-value [a]**
Time between appointments			
Baseline (initial appointment to date of intervention) in days, mean (SE)	-1.6 (2.2)	-5.9 to 2.7	0.45
Two month following the intervention in days, mean (SE)	-0.1 (2.5)	-5.0 to 4.8	0.96
Six months following the intervention in days, mean (SE)	0.75 (4.3)	-7.8 to 9.3	0.86

[a] Two-sample t-test assuming equal variances

Table 38 Regression model for the effect of the intervention on timing compliance, adjusted for time between practice visits

	Difference between means (%)	**95% CI (%)**	**p-value [a]**
'ITT' model (n=159)	-1.0	-5.1 to 3.1	0.63
Length of baseline period (N=154)	-0.8	-5.0 to 3.4	0.70
Length of two month follow-up in days (n=155)	-0.7	-4.9 to 3.5	0.75
Length of six month follow-up in days (n=156)	-0.4	-4.6 to 3.7	0.83

[a] Two-sample t-test assuming equal variances

Table 39 Regression model for the effect of the intervention on systolic blood pressure, adjusted for time between practice visits

	Difference between means (mmHg)	95% CI (mmHg)	p-value
'ITT' model (n=200)	-2.7	-7.2 to 1.8	0.24
Length of baseline period (N=193)	-1.9	-6.5 to 2.7	0.42
Length of two month follow-up in days (n=192)	-2.4	-6.9 to 2.2	0.31
Length of six month follow-up in days (n=195)	-2.3	-6.8 to 2.2	0.31

Table 40 Regression model for the effect of the intervention on diastolic blood pressure, adjusted for time between practice visits

	Difference between means (mmHg)	95% CI (mmHg)	p-value
'ITT' model (n=200)	0.2	-1.9 to 2.3	0.85
Length of baseline period (N=193)	0.1	-2.0 to 2.3	0.90
Length of two month follow-up in days (n=192)	-0.4	-2.2 to 2.1	1.0
Length of six month follow-up in days (n=195)	0.2	-2.0 to 2.3	0.88

7.5.3 Descriptive statistics for the intervention and control groups, taking account of process measures in the intervention group

As shown in Table 26 and Table 27 above, the number of patients who had in fact problems with taking their medication and subsequently received the 'full' intervention in terms of a strategy to address their medication problems, was relatively small. The number of participants in the intervention group who had at least one problem with their medication was 37 (28.9%), which means that only about one in three participants who were randomised to receive the intervention received adherence support in its true sense, whereas the remaining patients did not admit to any problems and therefore did not perceive themselves as requiring any further adherence support.

An obvious secondary analysis was therefore to investigate and compare descriptive statistics for the three groups of participants: (1) participants who were randomised to the intervention group, had problems with their medication and agreed a strategy to resolve these problems (these participants received the intervention as intended), (2) participants randomised to the intervention group who did not have any problems with their medication and therefore did not agree a strategy to resolve problems (these participants did not receive the intervention as intended), and (3) participants randomised to the control group (who may or may not have had problems with taking their medication).

Results of descriptive statistics for baseline and outcome variables comparing participants in terms of the 'amount' of intervention they have received are presented in Table 41. The percentages of men were slightly higher in the group of participants without medication problems (68.7%) and the usual care group (62.5%) compared with the group of participants in the intervention group who had medication problems (43.8%). Timing compliance was higher in the usual care group at baseline (94.5%) compared to the other two groups (88.2% for participants in the intervention group with medication problems and 92.0 for those without). At six months, timing compliance among participants in the intervention group who had medication problems (80.3%) was almost 10% lower than for the group who did not have medication problems and the usual care group (both 90.2%). There were no obvious differences in either systolic or diastolic blood pressure between the groups.

Table 41 Descriptive statistics for baseline and outcome variables comparing participants in the intervention group who did and did not have problems with their medication with participants receiving usual care

	Adherence support (participants with medication problems, n=32)	**Adherence support (participants without medication problems, n=96)**	**Usual care (n=117)**
Men, (%)	43.8 (14/32)	60.4 (58/96)	53.8 (63/117)
Age in years, mean ± SD	69.2 ± 12.2	67.5 ± 9.6	68.1 ± 9.4
Timing compliance at baseline (%), mean ± SD	88.2 ± 18.5	92.0 ± 14.3	94.5 ± 7.6
Timing compliance at 6 month follow-up (%), mean ± SD	80.3 ± 25.5	90.2 ± 16.6	90.2 ± 16.2
Systolic blood pressure at baseline (mmHg), mean ± SD	150.0 ± 17.5	148.0 ± 14.4	152.1 ± 17.5
Systolic blood pressure at 6 months follow-up (mmHg), mean ± SD	145.7 ± 22.2	141.8 ± 15.4	147.7 ± 20.9
Diastolic blood pressure at baseline (mmHg), mean ± SD	86.7 ± 8.5	82.7 ± 9.4	83.1 ± 9.9
Diastolic blood pressure at six months follow-up (mmHg), mean ± SD	83.8 ± 9.7	79.1 ± 10.1	79.9 ± 9.7

7.5.4 Subgroup analyses

Subgroup analyses were planned at the protocol stage and finalised in the study protocol before the trial was analysed. They were kept to a minimum and only included variables that were either stratifying variables, that is, age and sex, or other variables that based on the literature review could influence the effect of the intervention on the main outcomes, such as the total number of drugs a patient is taking or the drug group that was used in the electronic monitor. The following tables show the results for timing compliance, systolic and diastolic blood pressure at six months follow-up, stratified by age, sex, the total number of different drugs a patient is taking and the type of drug which was dispensed from the electronic monitor.

The following three tables present the results for timing compliance and blood pressure at six months, stratified by age. The effect of the intervention did not differ by age for timing compliance (interaction p=0.36), systolic blood pressure (interaction p=0.30) and diastolic blood pressure (interaction p=0.24).

Table 42 Mean (SD) timing compliance at six months follow-up in the intervention and control groups, stratified by age

	Adherence support	Usual care	p-value[a]
Age under 60	88.5 (20.7)	95.2 (5.4)	0.36
Age 60 or over in years	86.8 (20.1)	89.1 (17.6)	

[a] Test for interaction: coefficient 4.8, 95% CI -5.5 to 15.1

Table 43 Mean (SD) systolic blood pressure at six months follow-up in the intervention and control groups, stratified by age

	Adherence support	Usual care	p-value[a]
Age under 60	138.8 (13.8)	136.5 (10.4)	0.30
Age 60 or over in years	144.2 (18.5)	150.6 (21.1)	

[a] Test for interaction: coefficient -5.8, 95% CI -17 to 5.3

Table 44 Mean (SD) diastolic blood pressure at six months follow-up in the intervention and control groups, stratified by age

	Adherence support	Usual care	p-value[a]
Age under 60	87.8 (7.4)	85.1 (6.9)	0.24
Age 60 or over in years	78.0 (9.8)	78.6 (9.9)	

[a] Test for interaction: coefficient -3.2, 95% CI -8.6 to 2.2

The next three tables show mean timing compliance at six months follow-up, stratified by sex. These results show very weak evidence, that is, almost reaching statistical significance at the 5% level, that the treatment effect on timing compliance might differ by sex (interaction p=0.09, coefficient 7.0, SE 4.1, 95% CI -1.2 to 15.2). (Note that the

means given in these tables are crude values whereas the interaction coefficients are from the fully adjusted models.) This could point towards a potential interaction, in that women may be more likely to show increased adherence after the intervention than men. There were no differences between the sexes for systolic and diastolic blood pressure (interaction p=0.20 and 0.23 respectively).

Table 45 Mean (SD) timing compliance at six months follow-up in the intervention and control groups, stratified by sex

	Adherence support	**Usual care**	**p-value[a]**
Men	87.0 (20.0)	90.0 (15.8)	0.093
Women	87.4 (20.5)	90.6 (17.0)	

[a] Test for interaction: coefficient 7.0, 95% CI -1.2 to 15.2

Table 46 Mean (SD) systolic blood pressure at six months follow-up in the intervention and control groups, stratified by sex

	Adherence support	**Usual care**	**p-value[a]**
Men	143.3 (14.8)	145.8 (16.4)	0.20
Women	142.3 (20.8)	150.4 (25.7)	

[a] Test for interaction: coefficient -5.8, 95% CI -14.7 to 3.0

Table 47 Mean (SD) diastolic blood pressure at six months follow-up in the intervention and control groups, stratified by sex

	Adherence support	**Usual care**	**p-value[a]**
Men	80.7 (10.5)	79.8 (8.4)	0.23
Women	80.1 (9.7)	80.1 (11.3)	

[a] Test for interaction: coefficient -2.6, 95% CI -6.8 to 1.7

As shown in the following tables, the intervention effect differed neither by the number of different drugs that participants were prescribed, nor by the drug group dispensed through the electronic monitor.

Table 48 Mean (SD) timing compliance at six months follow-up in the intervention and control groups, stratified by total number of different drugs

	Adherence support	**Usual care**	**p-value[a]**
Total number of different drugs			
1-2	73.1 (28.0)	95.4 (5.3)	0.23
3-5	91.4 (13.1)	91.6 (15.0)	
6 or more	86.0 (23.4)	81.9 (25.3)	

[a] Test for interaction

Table 49 Mean (SD) systolic blood pressure at six months follow-up in the intervention and control groups, stratified by total number of different drugs

	Adherence support	**Usual care**	**p-value[a]**
Total number of different drugs			
1-2	136.8 (9.5)	141.6 (12.3)	0.99
3-5	145.6 (19.1)	151.9 (26.2)	
6 or more	145.1 (17.8)	149.7 (18.4)	

[a] Test for interaction

Table 50 Mean (SD) diastolic blood pressure at six months follow-up in the intervention and control groups, stratified by total number of different drugs

	Adherence support	**Usual care**	**p-value[a]**
Total number of different drugs			
1-2	80.3 (9.2)	82.7 (8.9)	0.45
3-5	80.5 (10.4)	79.2 (9.8)	
6 or more	80.3 (11.3)	77.1 (8.1)	

[a] Test for interaction

Table 51 Mean (SD) timing compliance at six months follow-up in the intervention and control groups, stratified by drug group

	Adherence support	**Usual care**	**p-value[a]**
Drug group			
Diuretic	88.0 (18.4)	87.3 (20.3)	0.12
Beta-blocker	92.0 (15.4)	95.2 (6.8)	
Calcium antagonist	82.7 (21.0)	92.3 (10.8)	
ACE inhibitor	83.9 (27.6)	94.2 (6.3)	
Other	79.6 (31.0)	92.8 (9.6)	

[a] Test for interaction

Table 52 Mean (SD) systolic blood pressure at six months follow-up in the intervention and control groups, stratified by drug group

	Adherence support	**Usual care**	**p-value[a]**
Drug group			
Diuretic	139.9 (16.1)	147.1 (18.8)	0.94
Beta-blocker	147.7 (19.1)	150.0 (33.8)	
Calcium antagonist	147.4 (17.1)	148.3 (16.4)	
ACE inhibitor	136.1 (17.9)	145.7 (11.1)	
Other	152.6 (17.3)	147.8 (11.3)	

[a] Test for interaction

Table 53 Mean (SD) diastolic blood pressure at six months follow-up in the intervention and control groups, stratified by drug group

	Adherence support	**Usual care**	**p-value[a]**
Drug group			
Diuretic	79.8 (11.0)	79.3 (11.0)	0.13
Beta-blocker	80.4 (8.0)	79.6 (9.1)	
Calcium antagonist	76.4 (9.7)	80.6 (8.4)	
ACE inhibitor	83.6 (12.3)	80.8 (8.0)	
Other	86.1 (10.1)	83.8 (6.2)	

[a] Test for interaction

7.6 Relationship between timing compliance and blood pressure

There was no evidence to suggest that in this study timing compliance was correlated with blood pressure. Notwithstanding the clear ceiling effects, Figure 25 and Figure 26 show that there are no obvious patterns in the scatter plots for the relationship between timing compliance, systolic and diastolic blood pressure (correlation coefficients -0.02 and -0.01, respectively).

Figure 25 Scatter plot of the relationship between timing compliance (y-axis, %) in the six months after the intervention and systolic blood pressure at the six month follow-up

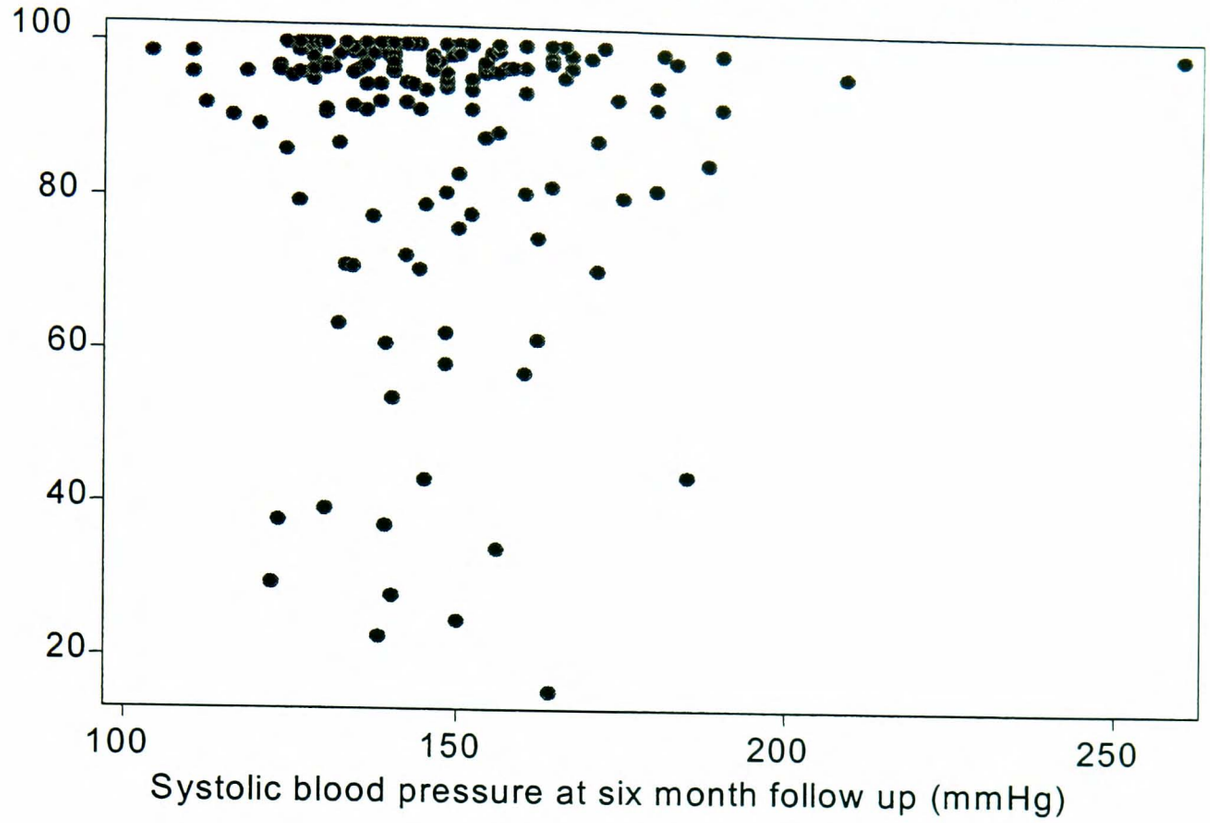


Figure 26 Scatter plot of the relationship between timing compliance (y-axis, %) in the six months after the intervention and diastolic blood pressure at the six month follow-up

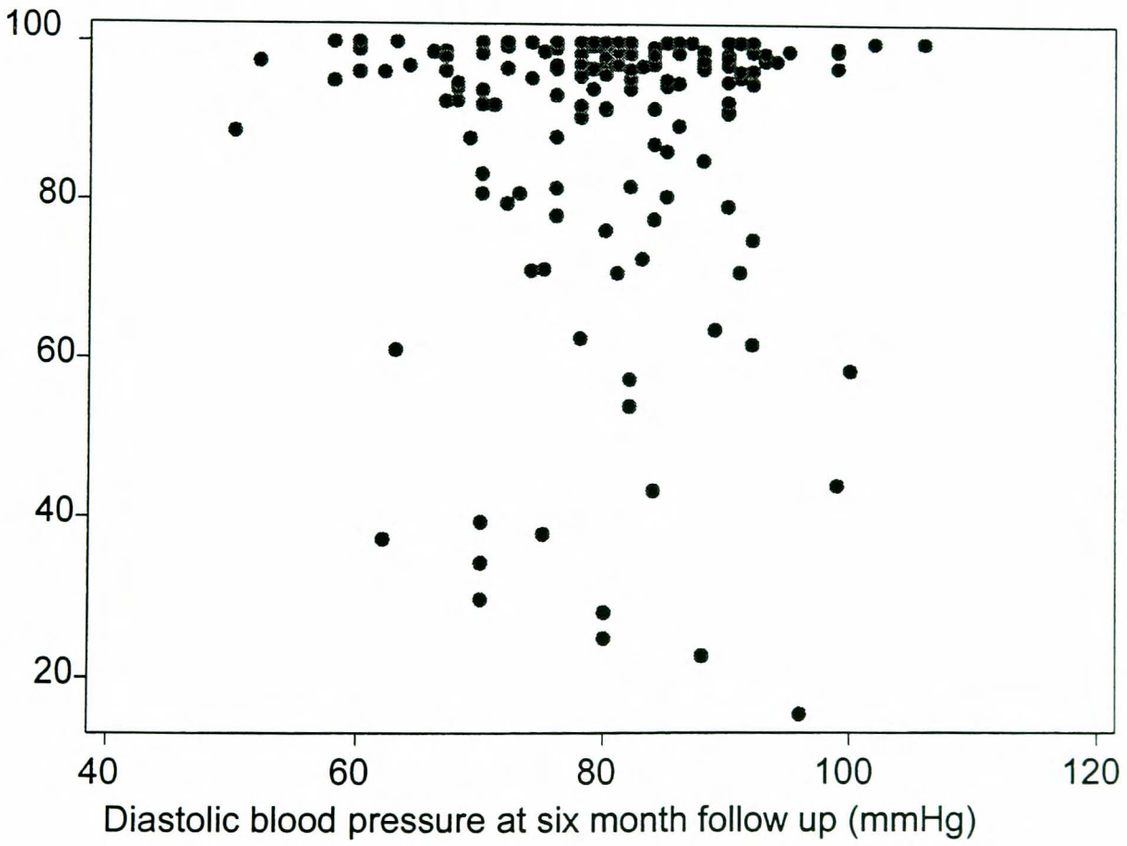


Table 54 shows the results of the regression model for the relationship between timing compliance and blood pressure at final follow-up. There was no evidence of an effect of

timing compliance on blood pressure for all participants combined or for any of the two intervention groups individually.

Table 54 Results of the regression model for the relationship between timing compliance in the six months after the intervention and blood pressure at the six month follow-up, controlling for age, sex and practice

	Difference between means (%)	95% CI	p-value
Systolic blood pressure			
All participants	0.02	-0.2 to 0.2	0.84
Control group	0.05	-0.2 to 0.3	0.67
Intervention group	-0.03	-0.2 to 0.2	0.80
Diastolic blood pressure			
All participants	0.01	-0.03 to 0.1	0.23
Control group	0.08	-0.05 to 0.2	0.24
Intervention group	0.03	-0.07 to 0.1	0.52

7.7 Summary

The aim of this open pragmatic randomised controlled trial was to evaluate the effectiveness of practice nurse-led adherence support on increasing adherence to blood pressure lowering medication in study participants with uncontrolled hypertension.

A total of 331 participants in 22 general practices in and around Bristol took part in the study. The practices, practice nurses and participants appeared broadly representative of respective populations in the UK.

The intervention was not effective in increasing adherence or in reducing blood pressure. There was no evidence of an effect of the intervention on timing compliance (difference between means: -1.0, 95% CI -5.1 to 3.1, p=0.63) or on less strict measures of adherence such as correct dosing (-0.5, 95% CI -4.2 to 3.1, p=0.77) or taking compliance (-0.6, 95% CI -3.2 to 4.4). There was also no difference between the groups in terms of systolic blood pressure (difference between means (mmHg): -2.7, 95% CI: -7.2 to 1.8, p=0.24) or diastolic blood pressure (0.2, 95% -1.9 to 2.3, p=0.85). In addition, neither of these differences is of important clinical significance.

Adjusting for variables that showed imbalance at baseline, which included (1) a history of cardiovascular disease, (2) use of over the counter medicines, (3) the total number of doses per day, (4) the drug grouped used in the electronic monitor, (5) the duration of blood pressure treatment, (6) a change in blood pressure medication in the past 12 months, (7) the reason for changing blood pressure medication during this period, and (8) self assessment of adherence did not substantially alter the findings from the primary analyses.

Pre-specified subgroup analyses showed that the intervention effect did not differ by age, the total number of drugs that were prescribed for a patient, and the drug group used in the electronic monitor. There was, however, very weak evidence of a possible interaction of sex on the effect of the intervention on timing compliance (interaction p=0.09, coefficient 7.0, SE 4.1, 95% CI -1.2 to 15.2), but not on systolic or diastolic blood pressure.

There was no evidence of a correlation or association of timing compliance in the six months after the intervention and blood pressure at the six month follow-up.

In conclusion, there was no evidence of a benefit or disbenefit of the intervention on timing compliance, systolic or diastolic blood pressure. In the following chapter I will present an economic evaluation of the trial intervention. I will then discuss the findings of these studies including the RCT with reference to existing knowledge in Chapter 9.

8 Economic evaluation: methods and results

8.1 Introduction

The previous chapter reported the results of a randomised controlled trial of the effect of nurse-led adherence support on medication adherence and blood pressure. The trial was pragmatic in that it evaluated the intervention in a realistic setting, so that in case the intervention was effective, it could be adopted into routine general practice.

In addition to evaluating the clinical effects of the intervention on medication adherence and blood pressure, it is also important to consider its cost implications and relative cost effectiveness in comparison with usual care. This economic evaluation mainly describes the costs incurred by the health service providers in primary care. As health care funding is limited, managers in general practice would want to know that any extra benefits from the intervention would be worth any additional expenses that may result from introducing nurse-led adherence support.

8.2 Methods

This section describes the methods used for this economic evaluation. Details about methodological issues that are relating to the conduct of the trial are described in chapters 5 and 6. These are not repeated here but will be referred to in the following sub-sections.

8.2.1 Objective

The objective of the economic evaluation described in this chapter was to compare outcomes and costs of usual care versus nurse-led adherence support (in addition to usual care) from the viewpoint of general practices.

8.2.2 Economic importance

Introducing nurse-led adherence support is likely to have resource implications, which would affect the choices decision-makers in general practice would have to make. Both alternatives, that is, maintaining the status quo in terms of usual care or adopting nurse-led adherence support, are realistic options, and conducting an economic analysis is therefore important.

8.2.3 Viewpoint of the economic evaluation

This economic evaluation has been conducted from the viewpoint of the provider institutions in the primary care sector. Managers in the primary care sector would be the key decision makers in deciding whether to introduce nurse-led adherence support into routine practice or to maintain the status quo and continue with usual care. The funding streams for nurses working in primary care follow various models, with nurses being employed by different organisations. For example, some practice nurses are directly employed by their general practice, which may be under the General Medical Services or the new Personal Medical Services Contract. Others are employed by the primary care trusts and, although working in the same building, are not directly accountable to their general practice. Therefore, this evaluation was carried out from the viewpoint of the primary care sector, which encompasses the various funding options. Although costs resulting from the adherence support intervention may also fall on patients, mainly in terms of time, and the wider NHS, in terms of hospital admissions or use of other NHS services, the focus of this chapter is on costs to the primary care sector only.

8.2.4 Selection of the alternative intervention

The choice of the alternative intervention, that is, usual care, was designed to get a close measure of the costs that would incur with introducing nurse-led adherence support, and both study interventions are described in detail in Chapter 5. Usual care, although differing to a certain extent from practice to practice, is obviously the most widely used alternative treatment.

8.2.5 Form of evaluation

The objective was to evaluate the cost-effectiveness of two alternative interventions, adherence support and usual care, which were evaluated in a pragmatic RCT. This trial found that the health effects of nurse-led adherence support and usual care were neither statistically nor clinically significantly different in terms of their effect on medication adherence and blood pressure. It was, therefore, more appropriate to use a cost-minimisation analysis rather than a cost effectiveness study. Costs are reported according to randomisation group.

8.2.6 Data collection

Details of the design and the results of the RCT, that is, the selection of study population, the method of allocating participants to a comparison group, analysis by intention-to-treat, and effect sizes with confidence intervals, are described in Chapters 5 and 6.

Identification of costs

The costs associated with usual care and additional nurse-led adherence support were identified in collaboration with a sample of the participating practice nurses and listed after a 'brain storming' exercise. Ideally, all resource use between randomisation and final follow-up should have been identified and collected, which would have included, for example, all GP consultations, the use of district nurses, costs associated with any medication changes resulting from the study intervention, hospital admissions and patient costs. However, collecting these data was either not feasible in this study or was relevant for viewpoints other than from the primary care sector perspective. Costs were further categorised into: (a) fixed costs, that is, those that do not vary with changes in treatment, (b) semi-fixed costs, which would include staff costs, and (c) variable cost, that is, those that vary directly with levels of the treatment like consultation times. The scope of this project did not allow the measurement of indirect costs and outcomes, which might, for example, have included time off work or away from other activities for the participating study participants. Any items that would not have occurred outside the trial were not relevant and were therefore excluded from the economic analysis. The major difference in cost between the two intervention groups was nursing time, which is the reason why this was included in the main analysis.

Measuring costs and outcomes

Data on resource use were collected by the participating practice nurses on data collection forms. This analysis primarily investigates the direct costs that result from the study intervention.

Generalisibility

The RCT included general practices in Avon that on the whole appear representative of practices in the UK (see chapter 6). In addition, this was a pragmatic RCT, which

increases the generalisibility of the study and therefore its value for an economic evaluation.

8.2.7 Resource use and costing

Interpreting the resource use as part of the trial was difficult, because the intervention that was tested in the RCT was complex. Nurse-led adherence support consisted of a number of different components, and everything done to a participant during the trial could have affected the main outcomes. Even visits to the surgery solely for data collection may have influenced medication adherence. For the purpose of this economic evaluation only the nurse time was costed, as this was the main factor determining costs as part of the intervention.

8.2.8 Training costs

Before the start of the trial I visited all participating practices and their practice nurses to explain the details of the trial and the alternative interventions. The nurses were provided a structured prompt sheet, which reminded them of the main barriers to medication adherence. I then explained to practice nurses the use of this prompt sheet for 10 minutes, but did not provide wider training on adherence-related issues (see Chapter 5 for further details). In essence, no formal training was provided for the practice nurses, since the intervention was designed to be pragmatic without the need for extensive training.

8.2.9 Consultation costs

Even without the intervention, patients normally visit the practices to consult either their GP or the practice nurse in connection with the management of their hypertension. Since most patients with uncontrolled hypertension require regular follow-up, with the frequency of visits depending on the blood pressure level and other risk factors, a change to nurse-led adherence support and the small number of extra visits was not expected to affect practice costs such as building maintenance or administrative staff costs substantially.

The lengths of the consultations of study participants with the practice nurses were obtained from the data collection sheets or from the practice computers. Practice nurses were asked to book patients in for the adherence support appointment for no longer than an additional 20 minutes, with 10 minutes allowed for the reinforcement appointment

two months later. The costs per minute of nurse consultation were taken from Unit Costs of Health and Social Care provided by the Personal Social Services Research Unit at the University of Kent.[270]

8.2.10 Main analysis

The primary outcomes for this economic evaluation are adherence to medication (timing compliance) and blood pressure (mmHg). Comparison between the groups in a pragmatic trial is a contrast between two policies or strategies of care. In a similar fashion as for the analysis of the main outcomes, comparing the two groups as randomised (on an intention-to-treat basis) means that the adherence support intervention is also costed just as one part of the intervention policy. Since both study interventions resulted in the same type of health gain in terms of the two main outcomes and the outcomes have been compared in an objective way, there is no need to value these benefits in monetary terms.

Since there was no evidence of a clinically or statistically significant effect of the nurse-led adherence support, neither on adherence nor blood pressure, a cost-minimisation analysis was performed. Information on resource use was calculated for each participant and reported by randomisation group.

The calculation of p-values in the context of this trial is of doubtful value because of the uncertainty surrounding the mean costs obtained for this study. Rather than addressing statistical imprecision, it seemed more important to use a sensitivity analysis to investigate uncertainties.

8.2.11 Sensitivity analysis

The estimation of the value of different parameters used in this economic evaluation was based on a number of assumptions. Unfortunately, data were not always complete, and some costs had to be calculated using arithmetic means across the practices. I therefore did not carry out statistical tests leading to confidence intervals.

Various approaches exist that can be used to perform sensitivity analyses. For example, one-way sensitivity analysis investigates in a systematic way the influence of each variable by varying it across a logical range of values, while all other variables are being held at their best estimate. In extreme scenario sensitivity analyses, each variable is being set to take the most optimistic or pessimistic value to generate a best or worst case

scenario. Probabilistic sensitivity is based on a number of simultaneous simulations, using various values of the underlying variables within a plausible range.

For this study I chose to use a simple one-way analysis, which is the most common type of analysis. This approach seemed the most appropriate for this study, as it allowed altering one or more variables to determine its effect on the final result. The sensitivity analysis included the duration of the appointments.

Scenario of different length and frequency of appointments

In the trial, the appointment length for the nurse-led adherence support was determined in close collaboration with the practice nurses, who estimated the time it would take them to talk about barriers to medication adherence. In addition, a two-month follow-up appointment was scheduled for every study participant in the intervention group regardless of whether there were any problems with medication taking or not. Since baseline adherence was high and the prevalence of medication problems was low in all study participants, the adherence support consultation could have been much shorter for the majority of patients. For these patients, the two-month reinforcement appointment was also unnecessary. In routine practice, adherence support could be provided as part of the ongoing care of hypertensive patients, with little extra time needed. This scenario assumes that the total time required to provide adherence support in addition to usual care lasted 20 minutes instead of 24.7 minutes (see Table 55).

8.2.12 Discounting

Although costs and benefits of the interventions may occur in the future in terms of increased or decreased medication usage or reduced incidence of cardiovascular events such as myocardial infarctions or strokes, this analysis does not discount costs and benefits to their present day equivalent value.

8.3 Results

In 10 out of the 21 practices taking part in the study, the practice nurses were employed by the Primary Care Trust, whereas in the remaining 11 practices, the practice nurses were paid by the practice. The main element of cost in the trial was the cost of extra consultation time in connection with delivering the adherence support intervention. Although I spent about 10 minutes with the practice nurses before the start of the trial

explaining how to use the prompt sheet, this did not consist of formal training on adherence related issues and was therefore not included in the analysis.

8.3.1 Extra consultation costs

The practice nurses spent on average an extra 13.4 minutes in direct patient contact in the intervention group (9.3 minutes for the adherence support intervention and 4.1 minutes for the reinforcement consultation), based on an average of 15.4 minutes in both the intervention and control groups. Table 55 shows the cost per consultation with the practice nurse from the perspective of the practices. The extra time spent in connection with the adherence support intervention almost doubled the costs for individual consultations.

Table 55 Costs per consultation with the practice nurse form the perspective of the practices

	Usual care	Adherence support
Usual time per standard consultation (minutes)	15.4	15.4
Extra time per adherence support consultation (minutes)	0	9.3
Extra time per reinforcement consultation (minutes)	0	4.1
Cost per minute [a]	£0.33	£0.33
Practice cost per consultation	£5.08	£9.50 [b]

[a] Consultation costs of nurses taken from Netten & Curtis[270], including both contact and non-contact time
[b] This is the total for the 'consultation package', that is, the adherence support consultation plus the additional reinforcement consultation

The time spent on writing to or telephoning patients to invite them for appointments or preparing for consultations was the same for both comparison groups and was not included in the analysis. If patients were invited by the receptionists, the time spent on this was also not included. No data were collected on the total time, including the waiting time, the study participants spent at the practice.

8.3.2 Sensitivity analysis

Table 56 presents the results of the sensitivity analysis in comparison with costs incurred in the control group and the costs that were observed in the trial, which would represent the likely maximum costs associated with the intervention. Assuming the scenario that the adherence support consultation lasted 20 minutes instead of 24.7 minutes and that no reinforcement appointment was provided reduces the practice costs per consultation by £2.90 to £6.60. However, the total costs are not reduced to the levels observed in the control group, since we would still expect practice nurses to spend some extra time on adherence support even in the absence of a formal adherence support consultation.

Table 56 and Table 57 provide the cost per nurse consultation under trial conditions as well as the projected cost per patient under a more realistic scenario, to help decision makers in general practice to extrapolate these results to their own setting. It should be possible to adapt these data to a range of different general practice settings, using local data on consultation and follow-up rates for hypertension. The practice protocols for follow-up of patients varied between practices in the trial. Whereas some practices followed up patients with uncontrolled hypertension at regular intervals, others used a more flexible approach depending on other cardiovascular risk factors, patient preferences, and response to treatment.

Table 56 Cost for the primary care sector per nurse consultation for the scenario, assuming a different duration of the adherence support consultation and no additional follow-up

	Control	Intervention	
		Observed	Projected
Costs for primary care sector per consultation	£5.08	£9.50	£6.60

8.3.3 Costs for the primary care sector

Table 57 shows the costs for the primary care sector, assuming average list sizes and numbers of uncontrolled hypertensive patients per general practice list. For practical reasons as outlined above, costs were calculated from the primary care sector perspective rather than distinguishing between general practices and, for example, primary care trusts.

Table 57 Total practice costs, assuming different numbers of patients with a diagnosis of hypertension per practice

Number of uncontrolled hypertensive patients per practice	Current policy (usual care)	Projected intervention costs (as in Table 56)	Projected additional costs per practice
235 (mean observed in the trial)	£1193.80	£1551.00	£357.20
130	£660.40	£858.00	£197.60
330	£1676.40	£2178.00	£501.60

8.3.4 Limitations

This study has only taken the viewpoint of general practices into account, and we did not obtain data on costs to patients (in terms of time off work or travel to practices). We also did not investigate cost implications for the wider NHS – for example, the intervention could have affected medication use on the whole or the number of hospital visits. 'Usual care' varied slightly between practices in terms of the protocols determining the frequency of follow up for hypertensive patients, which this economic analysis also did not take into account. Possible implications from these limitations are that they might introduce bias in terms of systematically overestimating or underestimating the costs of the intervention and that they might affect the precision of the results.

8.3.5 Summary

This chapter reported the results of an economic evaluation of a RCT of nurse-led adherence support for hypertensive patients in primary care. The results of this study showed that nurse-led adherence is more costly than usual care alone. There is no evidence to suggest that nurse-led adherence support is more efficient in improving medication adherence or reducing blood pressure than usual care. While some flexibility was considered within the sensitivity analysis, costing of other methods of delivering the intervention requires as well as their impact on prescribing costs and GP consultation rates require further research and development work.

In the following chapter I discuss the overall findings of the research described in this thesis in Chapter 9.

9 Discussion

9.1 Introduction

The previous chapters have desribed the theories behind research in adherence, the findings from past research, as well as the methods and results from individual studies that were conducted in the context of this thesis. In this chapter I briefly summarise the key findings again before considering the limitations of this study. Taking these limitations into account, I interpret the findings from this RCT and relate them to the results of previous research. Following on from this, I outline the implications of this thesis for clinical practice and future research. Finally I evaluate the overall contribution of this thesis.

9.2 Summary of the studies described in this thesis and their findings

The overall aim of this research was to find ways of helping hypertensive patients with taking their blood pressure lowering medication. Four studies contributed to this aim from different angles.

The systematic review synthesised the current evidence from RCTs on the effectiveness of interventions to increase adherence to blood pressure lowering medication. It highlighted strengths and weaknesses of such trials and provided the basis for the development of an intervention suitable for the UK primary care setting.

One of the main problems in adherence research is outcome measurement of adherence. A study comparing an adherence self-report tool with electronic monitoring was therefore conducted.

The RCT evaluated the effectiveness of a nurse-led adherence support intervention compared with usual care, followed by an evaluation of the economic implications of the intervention.

9.2.1 Summary of key findings from the systematic review

We conducted a systematic review of RCTs of interventions aiming to increase adherence to blood pressure lowering medication. This review suggests that simplification of dosing regimens appears to be the most promising intervention to

increase adherence in hypertension. There was mixed and inconclusive evidence for the effect of motivational and more complex interventions.

The trials included in this review were heterogeneous in terms of study populations, interventions and outcomes. The study populations included, for example, participants with newly diagnosed or established hypertension, who had either 'controlled' or 'uncontrolled' high blood pressure. Furthermore, the included studies tested a variety of different interventions, which we categorised into simplification of dose regimens, patient education, motivational strategies and more complex health and organisational interventions. Outcomes were measured in many different ways, including patient self-report, pill counts, drug blood levels or electronic monitoring. In addition, many studies were small and of poor methodological quality.

Due to clinical heterogeneity and the low overall quality of the studies, the results of this review should be interpreted with caution. The findings emphasized the need for further RCTs of adherence improving strategies in hypertension with sufficient power and of rigorous methodology.

9.2.2 Summary of key findings from the RCT

To my knowledge this was the first randomised trial of nurse-led adherence support in UK primary care. In addition, there has thus far not been an assessment of medication adherence in hypertension through electronic medication monitoring in the UK. The aim of this trial was to evaluate the effectiveness of practice nurse-led adherence support in increasing adherence to blood pressure lowering medication in study participants with uncontrolled hypertension, using a patient-centred and pragmatic approach.

In essence, this was a negative trial in terms of timing compliance as the primary outcome, and systolic and diastolic blood pressure as secondary outcomes. Baseline timing compliance was more than 90% and thereby high in both comparison groups, and mean blood pressure levels were close to the pre-specified cut-off point of ≥150/90 mmHg.

There was no evidence of an effect of the intervention on timing compliance or on the less strict measures of adherence such as correct dosing or taking compliance. There was also no difference between the groups in terms of systolic or diastolic blood

pressure. Additional adjustment for variables that showed any degree of imbalance at baseline did not alter the basic intention-to-treat model.

Pre-specified subgroup analyses showed that the effect of the intervention did not differ by age, the total number of drugs prescribed, or the drug group used in the electronic monitor. There was, however, very weak evidence of a possible interaction of sex on the effect of the intervention on timing compliance, but not on systolic or diastolic blood pressure. There was also no evidence of a correlation or association of timing compliance with blood pressure.

9.2.3 Summary of key findings from the economic evaluation

To consider the cost implications of nurse-led adherence support and its relative cost effectiveness in comparison with usual care we conducted an economic analysis. A change from usual care alone to introducing nurse-led adherence support in addition to usual care led to increased costs per practice per year, ranging between £357.20 for smaller numbers of hypertensive patients to £501.60 for larger numbers. This finding is based on the sensitivity analysis, which took into account a more realistic scenario. There is no evidence to suggest that nurse-led adherence support is a more efficient way of improving medication adherence or reducing blood pressure compared to usual care alone.

9.3 Limitations of the RCT

Every research study has its limitations, and it is important to recognise these when interpreting the findings. This study has a number of limitations, some of which could have affected the study results. For this reason I consider these limitations first before interpreting the results of this study.

9.3.1 Potential for response bias

Practices

Both general practices and eligible patients were invited to take part in this study, but not all invited practices and patients decided to take part. Only 23 out of 82 practices (23%) agreed to take part in this study, which raises the possibility of response bias in terms of practice recruitment. The overwhelming majority of practices who stated their reasons for not taking part in the study gave staff shortages and workload implications

as the main rationale for declining. There is no reason to believe that the practices that refused to take part were substantially and systematically different from the ones that took part. However, no data were available on the proportion of teaching practices in the UK, making a comparison with the trial practices difficult.

Study participants

Our recruitment strategy aimed to provide equal chances for all hypertensive patients registered with a surgery to be included in the study. Nearly one third of the eligible population (29%, 245/837) took part in our study. Since baseline blood pressures in both groups were close to our chosen cut-off point of ≥150/90, there is potential for response bias, as patients with higher blood pressures, who may also be less adherent to medication regimens, were perhaps less likely to take part in this study. Due to data protection reasons, I was unable to obtain data on eligible participants who refused to take part, which would have allowed an investigation of any systematic differences between these individuals and the study participants.

9.3.2 Potential for contamination

With the method of randomisation used in this trial, that is, randomisation by individual, there was potential for contamination. Because every practice had patients both in the intervention and control groups, this raised the possibility of participants in the control group inadvertently receiving the intervention. We were aware of this risk at the time we planned and designed this study. It was, therefore, decided to try to avoid this problem as much as possible by having separate nurses provide care for the intervention and control groups and by explicitly making the nurses aware of this risk and its possible implications for the validity of the study. Outcomes were, wherever possible, assessed by practice nurses not delivering the intervention. The median number of nurses per practice was 3.5 (range 1 to 7), which allowed the follow-up for both intervention groups to be conducted by different nurses in the majority of practices. The risk of contamination therefore seems relatively small, but would have been even smaller if this had been a cluster randomised trial.

9.3.3 Effect of electronic monitoring on adherence

Study participants were aware that medication adherence was assessed through the use of electronic medication monitors, thus raising the possibility of a Hawthorne effect, that is, the possibility that taking part in the study or using electronic monitors for

assessment of compliance may have changed study participants' behaviour. We do not know if and by how much the monitoring process, or indeed just taking part in this study, have affected the medication taking patterns of study participants. We were aware of this risk, which is one of the reasons why we followed study participants up for six months and tried to explain carefully to participants that this study was not about 'checking up' on them but to obtain more information on medication taking patterns. There is evidence from previous studies that adherence patterns change in terms of an increase in adherence around the dates of clinic visits. This change, however, is not usually sustained, and after about one week up to a maximum of four weeks most patients returned back to their usual medication-taking pattern.[101,132,266] We assumed that this effect would have occured in both the intervention and control groups and, therefore, investigated the differences between the groups, which should not have been affected in an important way by a general increase in adherence in both groups. However, in view of the skewed distribution of adherence data and high baseline adherence levels there is a possibility that, particularly in the region of higher timing compliance levels, this may have affected the study results, although this risk again is likely to be small.

9.3.4 Economic evaluation

This economic evaluation provides an approximation of the additional costs that practices would incur if they introduced nurse-led adherence support. This study focussed on the costs associated with nursing time, which appeared to be the main factor for additional practice expenses. However, the impact of the intervention on prescribing costs or GP time, which may have been positively or negatively affected, was not taken into account. Future studies of the economic consequences of adherence support interventions should take these factors into consideration.

9.4 Interpretation of the RCT results

Taking the limitations of this study into account, I discuss and interpret the results of the trial and the economic analysis in this section. I consider important issues in connection with the conduct of the study, and try to explain what the findings mean. This section starts by reflecting on issues affecting the internal validity of the study, before considering the wider generalisability of the study findings in terms of their external

validity. The internal validity is more important than the external validity, because it would be inappropriate to apply invalid findings to a wider population.[271]

9.4.1 Baseline comparability of study groups

There were no major differences between the comparison groups in terms of important clinical variables at baseline, and the groups were well balanced in this respect. Even where minor differences existed between the groups, adjusting for these factors in the regression analysis did not alter the results from the original intention-to-treat analysis, which suggests that the randomisation process was successful.

9.4.2 Losses to follow-up

Losses to follow-up were also similar for both groups, with no important differences between the groups in terms of age, sex, or differential losses to follow-up. However, there were differences in losses to follow-up between the practices. The main reason for this was that practice nurses left the practice or were off sick without passing on the responsibility for conducting the trial. There is no reason to believe that this has affected the study results as a whole, because these losses to follow-up were not caused by the study participants themselves. In addition, the practice nurses who stopped taking part in the study did not appear to be systematically different from the nurses completing the study.

9.4.3 Precision of the study

The total number of study participants randomised to the two comparison groups was 245, which was smaller than the pre-specified desired sample size of 330 participants. The trial did not show any evidence of an effect of the adherence support intervention on the primary outcome timing compliance compared with usual care, which raises the question as to whether this study may have been underpowered to detect a statistically significant difference between the two comparison groups with respect to the primary outcome.

Although the total number of study participants was smaller than expected, the results attained by this study were precise enough to counter this argument. The values of the confidence intervals for the primary outcome enable us to rule out a benefit or disbenefit in excess of about five percentage points in timing compliance, which is small and considerably lower than the target difference specified in advance.

The precision gained in this study highlights the uncertainty that surrounded the original power calculation in terms of the assumptions we made about the primary outcome. The findings from this study should, therefore, be useful for future power calculations that use timing compliance as the main outcome.

9.4.4 High baseline levels of timing compliance

During the planning stage of this trial we assumed, based on past research, that lack of adherence to blood pressure lowering medication is widespread. In particular, we assumed that it occured in 50% to 60% of all hypertensive patients, and that it is an important contributing factor for poor control of hypertension in the community.[2] However, baseline timing compliance in this RCT was much higher than expected with a mean timing compliance in both groups of over 90%. This is inconsistent with past research and an interesting finding, which I will discuss in more detail in Section 9.5 below. If baseline levels of adherence are already high, this obviously provides much less of an opportunity for further improvement compared with a situation where baseline adherence was lower.

The lack of an effect of the intervention in this study, therefore, needs to be seen in the context of already high adherence levels and is only generalisable to patients with high baseline timing compliance. We do not know what effect the intervention would have on people with lower adherence levels.

Since in our patient information sheet we informed prospective study participants that electronic monitors would be used to assess adherence, this could have deterred 'poor' adherers from taking part, who may have felt that they would appear to be 'failing' the GPs and practice nurses by not taking their medicines as prescribed.

Although the intervention was not successful in increasing overall adherence, a high percentage of the small number of participants who did have problems with their medication found the intervention effective (see Table 41). This raises the possibility that the intervention could be more effective in patients who indeed have problems with taking their medicines. An interesting observation was, however, that timing compliance dropped from 88.2% (SD 18.5) to 80.3% (SD 25.5) in this group, raising the possibility that although participants found the intervention helpful, the intervention may even have affected timing compliance in a negative way. These results have to be interpreted with caution due to the small number of individuals in the group who had medication problems.

9.4.5 Effectiveness of the intervention in subgroups of participants

There was very weak evidence, that is, almost reaching statistical significance at the 5% level, that the treatment effect of adherence support on timing compliance might differ by sex (interaction p=0.09, coefficient 7.0, SE 4.1, 95% CI -1.2 to 15.2), in that women may be more likely to show increased adherence after the intervention than men. Since this is the result of a subgroup analysis which can be unreliable, it has to be interpreted with extreme caution and should only be considered for the generation of new hypotheses.[254] However, this raises interesting questions as to whether there could be any differences between the sexes in their response to the intervention. All the practice nurses taking part in this research were female, and it is plausible that for various reasons men might respond differently to nurse-led adherence support than women.

9.4.6 Baseline blood pressure levels

We chose to recruit study participants with 'uncontrolled hypertension', using a widely agreed audit standard defined by the British Hypertension Society,[19] because we felt that increasing adherence in this group of patients was more important than in patients who are already well controlled. However, mean systolic and diastolic blood pressure in study participants were below or around the British Hypertension Society Audit Standard, which raises the question as to whether the study participants were at the lower end of the range of 'uncontrolled' blood pressures identified through the search of practice registers.

Unfortunately, for reasons of confidentiality and data protection we were unable to compare blood pressure levels of patients taking part in the study with those who declined to take part. Obviously, this leads to questions about the potential for response bias, which has already been discussed in Section 9.3.

9.4.7 External validity

The mean list sizes showed slight differences between the study practices and practices in Avon and the UK as a whole, but these were not excessive and unlikely to have affected the external validity of the study. We selected a random sample from identified eligible patients in the practice registers, stratified by age and sex. This process aimed to increase the external validity of the study by selecting study participants in an age/sex ratio similar to the national average. This process appeared to be successful and resulted in a representative sample in terms of the age/sex distribution.

9.5 Discussion of the results in the light of previous studies

9.5.1 Adherence levels in the community

Baseline timing compliance, the strictest measure of adherence obtained through electronic monitoring, was in excess of 90% in study participants, challenging the widespread belief that adherence to blood pressure lowering medication is only about 50-60%. However, this figure is based on studies that often used arguably unreliable methods of measuring adherence and that were mainly conducted in North America.[2,41] Our finding of much higher adherence than expected in the study population does not fit into the existing body of knowledge and is inconsistent with current theories.

However, when comparing the results of this RCT with the five trials of simplified dosing regimens included in our systematic review that have used MEMS® for outcome measurement of adherence, a different picture emerges. Andrejak and colleagues found that correct dosing, which is the second strictest adherence measure next to timing compliance, was between 78.1% and 94% during their study.[182] A trial by Mounier-Vehier and colleagues resulted in timing compliance between 74.8% and 92.5%.[189] Timing compliance in a study by Detry and colleagues was 52.8% and 78.7% in both comparison groups.[272] Leenen and colleagues found timing compliance to be between 74% and 93%.[188] Brigeen and colleagues reported timing compliance between 61.1% and 86.6% for both comparison groups.[190] It is worth pointing out that these results are data from the follow-up period, and comparison with the baseline data from our trial is therefore of limited value. However, the findings from these trials illustrate that even in the control groups timing compliance was between 52.8% and 78.1%, with three of the five trials showing mean timing compliance levels of 74% and over. These results confirm the doubts raised about the accuracy of the "average adherence of 50-60%" which is so often quoted.[2]

Of course, we do not know whether the high adherence levels observed in the RCTs described in this thesis and elsewhere were due to a self-selected population, or whether the results reflect generally higher adherence levels in the UK. This raises the question as to whether doctors and researchers in the UK have made the wrong assumptions about their patients' propensity for not taking their medicines as prescribed. Higher adherence levels in the UK would not be implausible, as the UK National Health Service is different from health care delivery in the US. Whereas patients in the UK only have to pay a prescription charge, hypertensive people in the US and Canada often

have to pay for their medicine, which might explain higher levels of non-adherence in North American settings. In addition, the UK is unique in its organisation of primary care, with GPs being in charge of the overall care of their patients, which could positively affect medication adherence.

9.5.2 Effectiveness of nurse-led care

The lack of an effect of nurse-led adherence support on timing compliance in this RCT is perhaps not altogether surprising, given the inconclusive evidence that has often been provided by past RCTs.[41]

There is evidence of potential benefits from nurse-led care in terms of improving adherence. Logan and colleagues compared worksite treatment in 457 untreated hypertensive patients aged 18 to 69 years with care by family physicians.[206] Study participants in the group receiving the nurse intervention were more likely to be started on blood pressure lowering medication (95% versus 63%), to reach the agreed target blood pressure (49% versus 28%), and to show greater medication adherence (68% versus 49%). In an RCT by Nessman and colleagues, nurses and psychologists taught study participants self-determination, resulting in participants in the intervention group being 'adherent' for 1.3 more weeks.[221] Phone calls in a trial by Kirscht and colleagues led to a 5% improvement in adherence ($p<0.05$).

Another trial by Logan and colleagues, however, did not find any evidence for an effect of nurse-led worksite care on adherence.[207] Oakeshott and colleagues conducted a review on the role of nurse-led blood pressure management in primary care on blood pressure control and prescribing.[65] This review concluded that nurse-led management of people with high blood pressure could lead to improvements due to strict adherence to protocols, agreed target blood pressure, better prescribing and adherence, and regular follow-up, but that the evidence to support this view is not very robust.

The RCT described in this thesis has provided some new evidence on the effectiveness of nurse-led care on adherence to blood pressure lowering medication. This trial is the first of its kind to measure baseline levels of adherence and compare these with adherence levels at follow-up. Our study provided some answers, but posed even more questions about the potential effectiveness of the intervention and adherence levels in the community. Possible approaches to answer these questions are further considered in Section 9.7 below.

9.6 Implications for practice

The results of this study do not support the introduction of nurse-led adherence support for the management of hypertension in UK primary care. In addition to the lack of an effect in terms of increasing adherence, introduction of nurse-led adherence support can also not be recommended for reasons of cost effectiveness. The costs of delivering the intervention estimated in the economic analysis was, however, based on a number of assumptions, and it is likely that the actual cost of introducing the intervention into routine practice would be different to the costs incurred in the trial. The sensitivity analysis used a more realistic scenario to increase the external validity of the costs and to provide a better estimate of costs that would incur in actual practice.

Although not based on evidence, there appear to be few reasons why practice nurses, or indeed GPs, should not routinely ask patients in more detail about their medication taking, particularly if they show a less than expected response to their medical treatment. The justification for this is that in the few study participants who did have medication problems, the intervention appeared to be very successful, although numbers were far too small to come to any robust conclusions. However, asking patients about their medication taking and trying to identify individual solutions could be performed opportunistically on selected patients with minimal extra costs and potential benefits in terms of improved adherence, better blood pressure control – and a possible improvement in communication between patient and health professional.

9.7 Implications for future research

The research in this thesis has created many more questions than answers, suggesting a number of new theories and hypotheses that should be further evaluated with appropriate research designs.

9.7.1 Identification of 'true' adherence levels

One of the most surprising findings of this thesis was that baseline adherence levels in this study were high in both groups, contrary to the common belief that average adherence levels are around 50-60%. This observation strongly suggests that further observational studies are required to investigate the epidemiology of adherence in treated hypertensive people in the UK. Previous studies often used varied and imprecise measurements and definitions of adherence and had relatively short follow-up periods.

Wherever possible, future studies should use reliable instruments to measure medication adherence such as electronic monitoring.

9.7.2 The potential use of the adherence self-report tool to differentiate between non-adherence and non-response

Clinically it can be very difficult to differentiate between non-adherence and non-response, but this distinction is very important, as it prompts entirely different management strategies. For this reason we would have ideally screened all potential trial participants for non-adherence prior to randomisation. One option would have been to use electronic monitoring, which has successfully been used by Burnier and colleagues in a hospital setting to differentiate between non-adherence and non-response.[172,173] There were two reasons why we did not screen for non-adherence with electronic monitors. First, the intervention was meant to be pragmatic. Electronic monitors have so far mainly been used as research tools. Their use of a screening tool in routine primary care in the forseeable future appeared unrealistic, which made us avoid using this method for screening purposes. Second, if electronic monitors were used to screen for non-adherence, this would have contributed to the intervention itself, in that nurses would have become aware of medication adherence in individual patients, which may have influenced the management of their patients. The concurrent use of electronic monitors as part of the intervention and as an instrument for outcome measurement would have made the trial much more complex, making it even more difficult to disentangle the effects of individual components of the intervention. It was, therefore, felt that the role of electronic monitoring for the purpose of this trial should be limited to outcome measurement of adherence only.

More research is thus needed on the use of a self-report tool to screen for non-adherence. Although the study described in Chapter 6 comparing a self-assessment tool with electronic montoring has shown interesting and promising results, these need to be further validated in a less selective study population outside trial conditions.

9.7.3 Evaluation of the intervention in patients with low adherence and/or higher blood pressure levels

The patients taking part in this trial were essentially well controlled in terms of their blood pressure levels and showed high adherence, providing little opportunity for any intervention aimed at improving adherence to show an effect. Future studies of adherence improving strategies should therefore concentrate on patient who have been

identified as being non-adherent. This might either be achieved by using electronic monitoring (so-called 'measurement-guided medication management'[172,173]) or screening by using an adherence self-report tool as described and evaluated in this thesis.

9.7.4 Evaluation of complex interventions in primary care

The World Health Organization and the Working Party on Concordance advocate a multidisciplinary approach to make progress in the area of improving medication adherence.[2,13] Once more is known about the epidemiology of adherence in UK primary care, future research should involve evaluation of complex interventions, which should also include nurse-led care.[65] Interventions should target those at greater levels of risk and always take patient preferences and concerns into account.[2]

Since the evaluation of complex interventions in randomised trials can be challenging, these should be rigorously developed in stages as advocated by the Medical Research Council.[233] The design of new interventions should be based on findings from both qualitative and quantitative research and needs to follow sequential phases including an exploration of the relevant theory, an identification of the components of the intervention, an exploratory trial and a definitive randomised controlled trial prior to an evaluation of the long term implementation. When designing and evaluating complex interventions, particular attention should be paid to selection bias, unmeasured contextual variables and uncontrolled interaction effects that arise because there is an interaction between the environment and the intervention.[234] Greater recruitment rates might be achieved by clear and accurate patient information and an opportunity for prospective study participants to discuss concepts such as randomisation, which many people find difficult to understand and which may deter them from taking part in a trial.[273]

If adherence levels in the UK are confirmed to be low, then there will be a need for pragmatic primary care based trials of adherence improving interventions.[2,41] Haynes remarked in an editorial on the testing of healthcare interventions that "we need more effectiveness studies to sort the fool's gold from the true gold and efficiency studies to tell us if the price of the extraction is a bargain".[274] In addition, it is important that future trials address the research needs of primary care and are relevant to patients.[275]

9.7.5 Relationship between adherence and blood pressure control

The lack of a simple relationship between adherence and blood pressure control, as demonstrated again in this trial, complicates the perceptions of patients and health professionals about the importance of complete adherence. Some medicines are very 'forgiving', that is, a change to the treatment regimen in terms of missed or delayed doses may not affect the outcomes assessed in the study and may go unnoticed.[88] Much more research is needed on the relationship between medication adherence and blood pressure control, which should involve researchers from multiple disciplines including, among others, pharmacologists, specialists in the field of hypertension, epidemiologists and clinicians.

9.7.6 Strategies used by patients for increasing adherence

Although many publications in the field of medication adherence have identified 'barriers to adherence', little is known about strategies that patients have adopted to deal with non-intentional non-adherence. Unlike exercise or diet, adherence to medication has so far rarely been recognised as a behavioural issue.[88] It is important to appreciate that the issue in improving adherence is not necessarily a change of patients' existing behaviour, but rather undertaking and getting accustomed to a new behaviour. There is thus a need for studies that investigate further the strategies that patients have already developed themselves, which might help inform the design of future interventions to improve adherence.

Future studies should try to obtain high response rates by addressing barriers to participation in randomised controlled trials. These may include lack of staff and training and time constraints on the part of the health professionals and additional demands of the trial, patient preferences, worry caused by uncertainty, concerns about patient information, consent or randomisation on the part of the patients.[276]

9.7.7 Economic evaluation

The intervention evaluated in the trial was complex in that it consisted of two separate appointments. There are different options for the duration and content of adherence support and subsequent follow-up. These would include not using a separate appointment, but providing adherence support opportunistically on an ongoing basis, which should be taken in to consideration in future studies.

The intervention may be more effective in patients with higher levels of blood pressure. If this was the case, then the intervention may become more cost-effective, because the additional costs per practice were not large.

9.7.8 Differentiation between different types of non-adherence

This trial did not take into account the different types of non-adherence, which require further study. These different types include erratic adherence and unwitting non-adherence, which can be described as 'non-intentional non-adherence'.[88] Some patients may deliberately choose to discontinue or alter a medical regimen because they believe that this is in their best interest, leading to more 'intentional' non-adherence. Future studies should take into account these different types of adherence. They need to include patient based outcome measures to find out what patients think about adherence improving strategies and and what influence interventions have on patients' quality of life.[277,278] Because adherence research is of direct relevance to patients, it is important to take patients' views into account when designing further qualitative and quantitative studies.[279,280]

9.8 The contribution of this thesis

9.8.1 Addressing the research aims

The overall aim of this thesis was to find ways of improving adherence to blood pressure lowering medication. The systematic review of RCTs was conducted according to standards set out by the Cochrane Collaboration and provided the latest evidence about the effetiveness of interventions to improve adherence in hypertension.

We developed a new six-point adherence self-assessment tool, which was validated against electronic monitors. To my knowledge, this is the first study that has developed a tool designed purely to detect non-adherence (in contrast to longer questionnaires that also try to shed light on the reasons for non-adherence) and validated this against the current 'gold standard'. The results of this study are promising and highlighted the need for further validation studies in more representative populations and in different chronic conditions. If the validity of the adherence self-report tool can be further established, then it might prove useful for clinicians in their day-to-day work by helping them to distinguish between non-adherence or non-response to medical treatment.

The results of the RCT described in this thesis did not show any evidence of an effect of nurse-led adherence support compared with usual care. However, these results may have been influenced by the high adherence and low blood pressure levels at baseline in both comparison groups. Potentially, nurse-led adherence support might be more effective in patients who do not take their tablets regularly and/or who have higher blood pressure levels at baseline. This view is supported by the fact that indeed in the few patients who had difficulty with their medication, the intervention appeared to be successful, although the numbers were too small to provide a robust conclusion.

9.8.2 Asking new questions

Overall, this study answered some questions, but it highlighted even more uncertainties. It produced new theories, particularly about the extent of non-adherence in UK primary care, which is an important result of this thesis. Theories are an important basis for clinical practice, health promotion and research, and it is essential to recognise new theories for scientific and practical reasons, as they can be immensely helpful in understanding healthcare.[281] What are the 'true' adherence levels in hypertensive people in the UK? Is nurse-led adherence support effective in people with low adherence and/or poor blood pressure control? What is the relationship between adherence and blood pressure control? How much adherence is enough to lead to the desired effect of the drug in question? How robust is the self-assessment tool of adherence outside a trial setting and in people with lower adherence? Is this tool useful in day-to-day clinical practice to distinguish between non-adherence and non-response? Are there ways to separate intentional from non-intentional non-adherers? How do patients feel about nurse-led adherence support? How do study participants feel about using the electronic monitors? Does nurse-led adherence support lead to better communication between patients and health professionals? These questions will be useful for formulating new hypotheses and theories, the answer to which might help patients with chronic diseases to have a better quality of life.

9.8.3 Future outlook

We have come some way to improve our understanding of adherence in hypertension, but much more work needs to be done to appreciate fully the issues in adherence research that are relevant to patients and health professionals alike. This need has been supported and summed up by a letter from one of the study participants that I received early in the study and with which I finish this chapter:

November 20th 2001

Dear Dr Schroeder

Thank you for your invitation to take part in your research concerning medication-taking in patients with high blood pressure.

I have signed the consent form (which I herewith enclose), though more from curiosity than for any other reason – I cannot imagine how such research can be anything other than using up money which might be better spent on some other project.

How can swallowing a pill at regular times, according to one's doctor's instructions, be made any easier?

One opens one's mouth, puts in the pill, swallows and takes a sip of water. Not so very difficult. If one's pill is taken at the same time every day, it's surely no hardship.

I rise every morning between 5.30 and 7.00, have a glass of grapefruit juice, a cup of coffee and a slice of dry toast with marmite or anchovy paste – swallow my pill and drink a glass of water (the slice of toast is simply because the pill should be taken after food – and I am thus reminded to take the thing, otherwise why would I be eating at that hour? One is not hungry at 7.00 in the morning).

Indeed I would be more interested in having explained to me, exactly what is high blood pressure and how does it work? (I understand about water pressure in taps – but do not understand what puts the pressure on blood – one cannot expect a busy general practitioner to make time to explain it). Neither do I understand how a dose of some chemical, taken orally, can affect this mysterious blood pressure – and why there should be so many different sorts and brand names – and, if they are so "good" and necessary, why are there so many ominous side effects, and so many restrictions on what one may take at the same time – i.e. pain killers, "cold cures", anti-inflammation pills to aid mobility, etc. (any of which one may need from time to time!).

I am naturally very reluctant to put anything into my body without knowing exactly what it is, how it works, and what it is likely to do to me. Only my fear of ending up like poor Princess Margaret [a] caused me to overcome my reluctance to start taking blood pressure tablets in the first place.

Even so, I think I was conned. I was not told that beginning this wretched treatment meant continuing with it forever, that I would be a slave to a pill-box for the rest of my life. I thought that this was a 'blip' and that once the pressure was reduced, I would be free again. Evidently not so.

I had had a heart scan on March 26th and my heart was functioning perfectly normally and the blood pressure was only very slightly high (I had been seeing the doctor fairly regularly about my "bad leg" – swollen ankles etc). And the pills are, of course, quite useless and taking them I became so lethargic I could no longer take my customary long walks, do the housework properly or even stay awake for any length of time. I would even fall asleep while sitting upright at my type-writer and indeed spent most afternoons and evenings lying on my back, fast asleep on the floor. What a waste of life. However, with determination, I have overcome this and now eight months later, can force myself to stay awake for most of the day. And my blood pressure continues to rise. Whatever it is, this 'blood pressure', there must be some other, better way of controlling it (this might be a suitable subject for research).

To return to the point – unfortunately nothing is easier than obediently swallowing a pill, whatever damage it may do to one's natural good health, and I fail to see how a (possibly costly) electronic pill-bottle can make it easier still.

Perhaps your research should be confined to such as are unable to follow simple instructions, perhaps through reasons of memory loss or one of the disabilities now lumped together as "learning difficulties" – but if you think my contribution would be of any use to you, I am prepared to go along with it. I am curious about the nature of your research and why one should think it is worth doing – but I still think it a sorry waste of money at a time when money is so important.

Yours faithfully

U.P.

[a] Princess Margaret endured poor health in the last years of her life. She was a heavy smoker, suffered at least two strokes, and died on 9 February 2002 aged 71.

10 Conclusion and recommendations

The overall aim of this thesis was to find ways of helping people suffering from high blood pressure with taking their blood pressure lowering medication. Four studies were carried out, which led to the following conclusions:

1. Based on a systematic review of RCTs, simplification of dosage regimes seems to be a useful strategy to increase adherence to blood pressure lowering medication. There is a need for further trials evaluating more complex interventions testing different educational and motivational strategies, which may be delivered by nurses and other allied health professionals. The results of this review have to be interpreted with caution due to the methodological shortcomings in many included trials.

2. A validation study of an adherence self-report tool compared with electronic monitoring showed that self-report can predict timing compliance at higher leveles of adherence. More research is needed on the usefulness of this tool in day-to-day practice and in a more representative study sample.

3. Nurse-led adherence support is no more effective than usual care in terms of increasing adherence or reducing blood pressure, based on the results from a RCT. Baseline adherence levels were high in both comparison groups, leaving little room for improvement. In the few participants who had medication problems, the intervention appeared to be successful, but further research is needed to further consolidate this finding.

4. There was no evidence from an economic evaluation that nurse-led adherence support was more cost-effective than usual care alone.

This thesis contributes to the literature on adherence by providing an up-to-date overview of evidence from past randomised trials on the effectiveness of interventions to improve adherence. Although the main study of this thesis, that is, the randomised trial, produced negative results, it raised questions about the 'true' level of adherence in the community and the potential effect of nurse-led adherence support in people with lower adherence or less well controlled blood pressure.

This thesis has developed many specific questions regarding the measurement of and scope for improving adherence to medication, which should be investigated in future research.

References

1. Haynes RB, Taylor WD, Sackett DL. Compliance in health care. Baltimore & London: The Johns Hopkins University Press; 1979.

2. Sabate E. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization; 2003.

3. Sheikh A, Smeeth L, Ashcroft R. Randomised controlled trials in primary care: scope and application. British Journal of General Practice 2002;52(9):746-51.

4. McGavock H, Britten N, Weinman J. A review of the literature on drug adherence. Royal Pharmaceutical Society of Great Britain; 1996.

5. Collins OR, Peto R. Antihypertensive drug therapy: effects on stroke and coronary heart disease. In: Swales JD, editor. Textbook of hypertension. Oxford: Blackwell Scientific Publications; 1994:1156-64.

6. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton JD et al. Blood pressure, stroke and coronary heart disease. Part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet 1990;335:765-74.

7. Psaty BM, Koepsell TD, Yanez ND, Smith NL, Manolio TA, Heckbert SR et al. Temporal patterns of antihypertensive medication use among older adults, 1989 through 1992. An effect of the major clinical trials on clinical practice? Journal of the American Medical Association 1995;273(18):1436-8.

8. Caro JJ, Speckman JL, Salas M, Raggio G, Jackson JD. Effect of initial drug choice on persistence with antihypertensive therapy: The importance of actual practice data. Canadian Medical Association Journal 1999;160(1):41-6.

9. Colhoun HM, Dong W, Poulter NR. Blood pressure screening, management and control in England: results from the health survey for England 1994. Journal of Hypertension 1998;16:752.

10. Sackett DL, Haynes RB, Gibson ES, Hackett BC, Taylor DW, Roberts RS et al. Randomised clinical trial of strategies for improving medication compliance in primary hypertension. Lancet 1975;1:1205-7.

11. Burt VL, Cutler JA, Higgins M, Horan MJ, Labarthe D, Whelton P et al. Trends in the prevalence, awareness, treatment, and control of hypertension in the adult US population. Hypertension 1995;26:60-9.

12. McDonald HP, Garg AX, Haynes RB. Interventions to enhance patient adherence to medication prescriptions: scientific review. Journal of the American Medical Association 2002;288(22):2868-79.

13. Marinker M, Blenkinsopp A, Bond C, Britten N, Feely M, George C et al. From compliance to concordance - achieving shared goals in medicine taking. London: Royal Pharmaceutical Society of Great Britain; 1997.

14. Adams F. Genuine works of Hippocrates. Melbourne: Krieger Publishing; 1972.

15. Schroeder K, Fahey T, Ebrahim S. Interventions to improve adherence to blood pressure lowering medication. A systematic review. Archives of Internal Medicine 2003;in press.

16. Swales JD. Guidelines on guidelines [editorial]. Journal of Hypertension 1993;11(9):899-903.

17. Fahey T, Peters TJ. What constitutes controlled hypertension? Patient based comparison of hypertension guidelines. British Medical Journal 1996;313:93-6.

18. Joint National Committee. The seventh report of the joint national committee on prevention, detection, evaluation and treatment of high blood pressure. Journal of the American Medical Association 2003;289:2560-72.

19. Ramsey LE, Williams B, Johnston G, MacGregor G, Poston L, Potter J et al. Guidelines for the management of hypertension: report of the third working party of the British Hypertension Society. Journal of Human Hypertension 1999;13:569-92.

20. Department of Health. Annual report of the Chief Medical Officer. High blood pressure - ending the rule of halves. London: Department of Health; 2003.

21. Fahey T, Schroeder K. High blood pressure. In: Jones R, Hobbs R, editors. Oxford Textbook of Primary Medical Care. 1st ed. Oxford: Oxford University Press; 2003.

22. Mulrow CD. Evidence-based hypertension. London: BMJ Books; 2001.

23. Swales JD. Textbook of hypertension. Oxford: Blackwell Scientific Publications; 1994.

24. Reeves R. Does this patient have hypertension? How to measure blood pressure. Journal of the American Medical Association 1995;273:1211-8.

25. Department of Health. National Service Framework for Coronary Heart Disease. London: HMSO; 2000.

26. Department of Health. National Service Framework for Older People. London: Department of Health; 2001.

27. Kaplan NM. The 6th Joint National Committee report (JNC-6): New guidelines for hypertension therapy from the USA. Keio Journal of Medicine 1998;47(2):99-105.

28. Hooper L, Bartlett C, Davey Smith G, Ebrahim S. Systematic review of long term effects of advice to reduce dietary salt in adults. British Medical Journal 2002;325:628-32.

29. Blumenthal JA, Sherwood A, Gullette ECD, Babyak M, Waugh R, Georgiades A et al. Exercise and weight loss reduce blood pressure in men and women with mild hypertension. Archives of Internal Medicine 2000;160:1947-58.

30. Whelton SP, Chin A, Xin X, He J. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized controlled trials. Annals of Internal Medicine 2002;136:493-503.

31. Ebrahim S, Davey Smith G. Systematic review of randomised controlled trials of multiple risk factor interventions for preventing coronary heart disease. BMJ 1997;314:1666-74.

32. The ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. Journal of the American Medical Association 2002;288(23):2981-97.

33. Philipp T, Anlauf M, Distler A, Holzgreve H, Michaelis J, Wellek S et al. Randomised, double blind, multicentre comparison of hydrochlorothiazide, atenolol, nitrendipine, and enalapril in antihypertensive treatment: results of the HANE study. HANE Trial Research Group. British Medical Journal 1997;315:154-9.

34. Bloom BS. Daily regimen and compliance with treatment: fewer daily doses and drugs with fewer side effects improve compliance. British Medical Journal 2001;323:647.

35. Hansson L, Lindholm LH, Ekbom T, Dahlof B, Lanke J, Schersten B. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity in the Swedish Trial in old patients with hypertension-2 study. The Lancet 1999;354:1751-6.

36. Brown MJ, Cruickshank JK, Dominiczak AF, MacGregor GA, Poulter NR, Russell GI, Thom S, Williams B. Better blood pressure control: how to combine drugs. Journal of Human Hypertension 2003;17:81-86.

37. Staessen J, Wang J-G, Thijs L. Cardiovascular protection and blood pressure reduction. The Lancet 2001;358:1305-15.

38. Vidt DG. New strategies for blood pressure control. Journal of Human Hypertension 2002;16(Suppl 1):S124-S127.

39. Mulrow CD, Lau J, Cornell JA, Brand M. Pharmacotherapy for hypertension in the elderly (Cochrane Review). In: The Cochrane Library, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd.

40. Forette F, Seux M-L, Staessen J, Thijs L , Babarskiene M-R, Babeanu S et al. The prevention of dementia with antihypertensive treatment. Archives of Internal Medicine 2002;162:2046-52.

41. Ebrahim S. Detection, adherence and control of hypertension for the prevention of stroke: A systematic review. Health Technology Assessment 1998;2(11).

42. O'Rorke JE, Richardson WS. Evidence based management of hypertension: what to do when blood pressure is difficult to control. British Medical Journal 2001;322:1229-32.

43. Fahey T, Schroeder K, Ebrahim S. Systematic review of organisation and delivery of care interventions used to improve the control of blood pressure in patients with hypertension. Submitted for publication to Archives of Internal Medicine 2003.

44. Hypertension Detection & Follow-up Program. Results and implications of the Hypertension Detection and Follow-up Program. Progress in Cardiovascular Diseases 1986;29(3 Suppl 1):1-124.

45. Hobbs FDR. The new British Hypertension Society Guidelines: a view from primary care. Journal of Human Hypertension 2000;14(223):225.

46. Cranney M, Barton S, Walley T. Auditing the management of hypertension in British general practice: a critical literature review. British Journal of General Practice 1998;48:1424-8.

47. Alderman MH, Lamport B. Labelling of hypertensives: a review of the data. Journal of Clinical Epidemiology 1990;43(2):195-200.

48. Wood D, De Backer G, Faergeman O, Graham I, Mancia G, Pyorala K. Prevention of coronary heart disease in clinical practice: recommendations of the Second Joint Task Force of European and other Societies on Coronary Prevention. Atherosclerosis 1998;140:199-270.

49. Jackson R. Guidelines on preventing cardiovascular disease in clinical practice. British Medical Journal 2000;320:659-61.

50. Brindle P, Fahey T. Primary prevention of coronary heart disease . British Medical Journal 2002;325:56-7.

51. McManus RJ, Mant J, Meulendijks CFM, Salter RA, Pattison HM, Roalfe AK et al. Comparison of estimates and calculations of risk of coronary heart disease by doctors and nurses using different calculation tools in general practice: cross sectional study. British Medical Journal 2002;324:459-64.

52. Mant J, Murphy M, Rose P, Vessey M. The accuracy of general practitioner records of smoking and alcohol use: comparison with patient questionnaires. Journal of Public Health Medicine 2000;22(2):198-201.

53. Peters TJ, Montgomery AA, Fahey T. How accurately do primary health care professionals use cardiovascular riks tables in the management of hypertension? British Journal of General Practice 1999;49:987-8.

54. Law MR, Wald NJ. Risk factor thresholds: their existence under scrutiny. British Medical Journal 2002;324:1570-6.

55. Alderman MH, Furber CD, Kostis JB, Laragh JH, Psaty BM, Ruilope LM et al. Hypertension guidelines: criterial that might make them more useful. American Journal of Hypertension 2002;15:917-23.

56. Steel N. Thresholds for taking antihypertensive drugs in different professional and lay groups: questionnaire survey. British Medical Journal 2000;320:1446-7.

57. Padwal R, Straus SE, McAlister F. Cardiovascular risk factors and their effects on the decision to treat hypertension: evidence based review. British Medical Journal 2001;322:977-80.

58. Pignone M, Mulrow CD. Using cardiovascular risk profiles to individualise hypertensive treatment. British Medical Journal 2001;322:1164-6.

59. Iliffe S. Nursing and the future of primary care. British Medical Journal 2000;320:1020-1.

60. Beecham L. UK health secretary wants to liberate nurses' talents. British Medical Journal 2000;320:1025.

61. Horrocks S, Anderson E, Salisbury C. Systematic review of whether nurse practitioners working in primary care can provide equivalent care to doctors. British Medical Journal 2002;324:819-23.

62. Salvage J, Smith R. Doctors and nurses: doing it differently. British Medical Journal 2000;320:1019-20.

63. Shum C, Humphreys A, Wheeler D, Cochrane M-A, Skoda S, Clement S. Nurse management of patients with minor illness in general practice: multicentre, randomised controlled trial. British Medical Journal 2000;320:1038-43.

64. Kinnersley P, Anderson E, Parry K, Clement J, Archard L, Turton P et al. Randomised controlled trial of nurse practitioner versus general practitioner care for patients requesting "same day" consultations in primary care. British Medical Journal 2000; 320:1043-8.

65. Oakeshott P, Kerry S, Austin A, Cappucio F. Is there a role for nurse-led blood pressure management in primary care? Family Practice 2003;20(4):469-73.

66. McHugh F, Lindsay GM, Hanlon P. Nurse-led care shared care for patients on the waiting list for coronary artery bypass surgery: a randomised controlled trial. Heart 2001;86:317-23.

67. Metry J-M. Measuring compliance in clinical trials and ambulatory care. In: Metry J-M, Meyer U, editors. Drug regimen compliance - issues in clinical trials and patient management. Chichester: Wiley&Sons;1999:1-21.

68. Steiner JF, Earnest MA. The language of medication taking. Annals of Internal Medicine 2000;132(11):926-30.

69. Dieppe P, Horne R. Soundbites and patient centred care. British Medical Journal 2002;325:605.

70. Wright EC. Non-compliance - or how many aunts has Matilda? The Lancet 1993;342:909-13.

71. Donovan JL, Blake DR. Patient non-compliance: deviance or reasoned decision-making. Social Science and Medicine 1992;34(5):507-13.

72. Waeber B, Brunner HR, Metry J-M. Compliance with antihypertensive treatment: implications for practice. Blood pressure 1997;6:326-31.

73. Caro JJ, Salas M, Speckman JL, Raggio G , Jackson JD. Persistence with treatment for hypertension in actual practice. Canadian Medical Association Journal 1999;160(1):31-7.

74. Jones JK, Gorkin L, Lian JF, Staffa JA, Fletcher AP. Discontinuation of and changes in treatment after start of new courses of antihypertensive drugs: a study of a United Kingdom population. British Medical Journal 1995;311:293-5.

75. Urquhart J. Role of patient compliance in clinical pharmacokinetics: review of recent research. Clinical Pharmacokinetics 1994;27(202):215.

76. Playle JF. Concepts of compliance: understandings and approaches. The British Journal of Family Planning 2000;26(4):213-9.

77. Marinker M. Personal paper: Writing prescriptions is easy. British Medical Journal 1997;314:747-8.

78. Mullen P. Compliance becomes concordance. Making a change in terminology produce a change in behaviour. British Medical Journal 1997;314:691-2.

79. Marinker M, Shaw J. Not to be taken as directed: putting concordance for taking medicines into practice. British Medical Journal 2003;326:349-50.

80. Brawley LR, Culos-Reed SN. Studying adherence to therapeutic regimens: overview, theories, recommendations. Controlled Clinical Trials 2000;21:156S-63S.

81. Kruse WHH. Compliance with treatment of hyperlipoproteinaemia in medical practice and clinical trials. In: Cramer JA, Spilker B, editors. Patient compliance in medical practice and clinical trials. New York: Raven Press; 1991. p. 175-86.

82. Vitolins MZ, Rand CS, Rapp SR, Ribisl PM , Sevick MA. Measuring adherence to behavioral and medical interventions. Controlled Clinical Trials 2000;21:188S-94S.

83. Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. Clinical Therapeutics 1999;21(6):1074-90.

84. Pullar T, Feely MP. Reporting compliance in clinical trials. Lancet 1990;336:1252-3.

85. Beardon PHG, McGilchrist MM, McKendrick AD, McDevitt DG, MacDonald TM. Primary non-compliance with prescribed medication in primary care. British Medical Journal 1993;307:846-8.

86. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Medical Care 1986;24(1):67-74.

87. Steele DJ, Jackson TC, Gutmann MC. Have you been taking your pills? The adherence-monitoring sequence in the medical interview. Journal of Family Practice 1990;30(3):294-9.

88. Ellis S, Shumaker S, Sieber W, Rand C, and the pharmacological Intervention Working Group. Adherence to pharmacological interventions: current trends and future directions. Controlled Clinical Trials 2000;21:218S-25S.

89. Svarstad BL, Chewning BA, Sleath BL, Claesson C. The brief medication questionnaire: a tool for screening patient adherence and barriers to adherence. Patient Education and Counseling 1999;37:113-24.

90. de Klerk E. Patient compliance in rheumatology: experiences with an electronic monitoring device. University of Maastricht; 2002.

91. Pullar T, Kumar S, Tindall H, Feely M. Time to stop counting the tablets? Clinical Pharmacology and Therapeutics 1989;46:163-8.

92. Rudd P, Byyny RL, Zachary V, LoVerde ME , Titus C, Mitchell WD et al. The natural history of medication compliance in a drug trial: limitations of pill counts. Clinical Pharmacology & Therapeutics 1989;46(2):169-76.

93. Cramer JA, Mattson RH, Prevey ML, Scheyer RD, Oulette VL. How often is medication taken as prescribed? A novel assessment technique. Journal of the American Medical Association 1989;261:3273-7.

94. Lee JY, Kusek JW, Greene PG, Bernhard S , Norris K, Smith D et al. Assessing medication adherence by pill count and electronic monitoring in the African American Study of Kidney Disease and Hypertension (AASK) Pilot Study. American Journal of Hypertension 1996;9(8):719-25.

95. Rudd P, Ahmed S, Zachary V, Barton C, Bonduelle D. Improved compliance measures: applications in an ambulatory hypertensive drug trial. Clinical Pharmacology & Therapeutics 1990;48(6):676-85.

96. Stephenson BJ, Rowe BH, Haynes RB, Macharia WM, Leon GL. Is this patient taking the treatment as prescribed? Journal of the American Medical Association 1993;269(21):2779-81.

97. Haynes RB, Taylor DW, Sackett DL, Gibson ES, Bernholz CD, Mukherjee et al. Can simple clinical measurements detect patient noncompliance? Hypertension 1980;2(6):757-64.

98. Cramer JA, Scheyer RD, Mattson RH. Compliance declines between clinic visits. Archives of Internal Medicine 1990;150:1509-10.

99. Feinstein AR. On white-coat effects and the electronic monitoring of compliance. Archives of Internal Medicine 1990;150:1377-8.

100. Kruse W, Weber E. Dynamics of drug regimen compliance: its assessment by microprocessor-based monitoring. European Journal of Clinical Pharmacology 1990;38:561-5.

101. Urquhart J. The electronic medication event monitor - lessons for pharmacotherapy. Clinical Pharmacokinetics 1997;32:345-56.

102. Waeber B, Vetter W, Darioli R, Keller U , Brunner HR. Improved blood pressure control by monitoring compliance with antihypertensive therapy. International Journal of Clinical Practice 1999;53(1):37-8.

103. Mallion JM, Baguet JP, Siche JP, Tremel F, de Gaudemaris R. Compliance, electronic monitoring, and antihypertensive drugs. Journal of Hypertension 1997;16(Suppl 1):S75-S80.

104. Nuesch R, Schroeder K, Dieterle T, Martina B, Battegay E. Relation between insufficient response to antihypertensive treatment and poor compliance with treatment: A prospective case-control study. British Medical Journal 2001;323(7305):142-6.

105. Schroeder K, Montgomery A, Ebrahim S. Pharmacological properties of antihypertensive drugs need to be acknowledged (letter). BMJ 2001;323:1129-30.

106. Vrijens B, Goetghebeur E. Comparing compliance patterns between randomized treatments. Controlled Clinical Trials 1997;18(3):187-203.

107. Rudd P. Clinicians and patients with hypertension: unsettled issues about compliance. American Heart Journal 1995;130(3):572-9.

108. Cramer JA, Spilker B. Patient compliance in medical practice and clinical trials. New York: Raven Press;1991.

109. Cramer JA, Mattson RH. Monitoring compliance with antiepileptic drug therapy. In: Cramer JA, Spilker B, editors. Patient compliance in medical practice and clinical trials. New York: Raven Press; 1991. p. 123-37.

110. Bosley CM, Parry DT, Cochrane GM. Patient compliance with inhaled medication: does combining beta-agonists with corticosteroids improve compliance? European Respiratory Journal 1994;7:504-9.

111. Maenpaa H, Manninen V, Heinonen OP. Compliance with medication in the Helsinki Heart Study. European Journal of Pharmacology 1992;42:15-9.

112. Rudd P, Ahmed S, Zachary V, Barton C, Bonduelle D. Improved compliance measures: applications in an ambulatory hypertensive drug trial. Clinical Pharmacology and Therapeutics 1990;48(6):676-85.

113. Vanhove TF, Schapiro JM, Winters MA, Merigan TC, Blaschke TF. Patient compliance and drug failure in protease inhibitor monotherapy. Journal of the American Medical Association 1996;276:1955-6.

114. Claxton AJ, Cramer J, Pierce C. A systematic review of the association between dose regimens and medication compliance. Clinical Therapeutics 2001;23(8):1296-310.

115. Britten N. Lay views of drugs and medicines: orthodox and unorthodox accounts. In: Williams SJ, Calnan M, editors. London: UCL Press; 1996.

116. Britten N. Patients' ideas about medicines: a qualitative study in a general practice population. British Journal of General Practice 1994;44:465-8.

117. Campbell R, Evans M, Tucker M, Quilty B , Dieppe P, Donovan JL. Why don't patients do their exercises? Understanding non-compliance with physiotherapy in patients with osteoarthritis of the knee. Journal of Epidemiology and Community Health 2001;55:132-8.

118. Kidd KE, Altman D. Adherence in social context. Controlled Clinical Trials 2000;21:184S-7S.

119. Horne R. Representation of medication and treatment: advances in theory and measurement . In: Petrie K, Weinman J, editors. London: Harwood Academic; 1997.

120. Lorish CD, Richards B, Brown S. Perspective of the patient with rheumatoid arthritis on issues related to missed medication. Arthritis Care and Research 1990;3:78-84.

121. Morgan M, Watkins CJ. Managing hypertension: beliefs and responses to medication among cultural groups. Sociology of Health and Illness 1988;10:561-78.

122. Morgan M. Perceptions and use of antihypertensive drugs among cultural groups. In: Williams SJ, Calnan M, editors. Modern medicine - lay perspectives and experiences. London: UCL Press Limited; 1996. p. 95-116.

123. Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication. Psychology and Health 1999;14:1-24.

124. Bandura A. Social foundations of thought and action. New York: Prentice-Hall; 1986.

125. Marlatt GA, Gordon JR. Relapse prevention: maintenance strategies in the treatment of addictive behaviours. New York: Guilford; 1985.

126. Prochaska JO, DiClemente CC. Stages of change in the modification of problem behaviours. In: Herten M, Eisler RM, Miller PM, editors. Progress in behaviour modification, 28. Sycamore: Terre Haute; 1992.

127. Janz NK, Becker M. The health belief model: a decade later. Health Education Quarterly 1984;11:1-47.

128. Leventhal H, Cameron L. Behavioural theories and the problem of compliance. Patient Education and Counselling 1987;10:117-38.

129. Leventhal H, Meyer D, Nerenz D. The common sense representation of illness danger. In: Rachman S, editor. Contributions to Medical Psychology. Oxford: Pergamon Press; 1980.

130. Leventhal H, Diefenbach M, Leventhal E. Illness cognition: using commonsense to understand treatment adherence and affect-cognition interactions. Cognitive Research and Therapy 1992;16(2):143-63.

131. Dowell J, Jones A, Snadden D. Exploring medication use to seek concordance with 'non-adherent' patients: a qualitative study. British Journal of General Practice 2002;52:24-32.

132. Urquhart J, de Klerk E. Contending paradigms for the interpretation of data on patient compliance with therapeutic drug regimens. Statistics in Medicine 1998;17:251-67.

133. Urquhart J. Time to take our medicines seriously. Pharmaceutisch Weekblad 1992;127:769-76.

134. Kleinbloesem CH, van Brummelen P, Danhof M, Faber H, Urquhart J, Breimer DD. Rate of increase in the plasma concentration of nifedipine as a major determinant of its haemodynamic effects in humans. Clinical Pharmacology and Therapeutics 1987;41:26-30.

135. Potter LS. Oral contraceptive compliance and its role in the effectiveness of the method. In: Cramer JA, Spilker B, editors. Compliance in medical care and clinical trials . New York: Raven Press; 1991. p. 195-207.

136. British Medical Association and The Royal Pharmaceutical Society of Great Britain. British National Formulary. 2003.

137. Inui TS, Carter WB, Pecoraro RE, Pearlman RA, Dohan JJ. Variations in patient compliance with common long-term drugs. Medical Care 1980;18(10):986-93.

138. Sullivan S, Kreling D, Hazlet T. Noncompliance with medication regimens and subsequent hospitalizations: a literature analysis and cost of hospitalization estimate. Journal of Research in Pharmaco-Economics 1990;2(2):19-33.

139. Cleemput I, Kesteloot K, DeGeest S. A review of the literature on the economics of noncompliance. Room for methodological improvement. Health Policy 2002;59:65-94.

140. Hughes D, Bagust A, Haycox A, Walley T. Accounting for noncompliance in pharmacoeconomic evaluations. Pharmacoeconomics 2001;19 (12):1185-97.

141. Sieber WJ, Kaplan RM. Informed adherence: the need for shared medical decision making. Controlled Clinical Trials 2000;21:233S-40S.

142. Stewart M. Towards a global definition of patient centred care. British Medical Journal 2001;322:444-5.

143. Jones G. Prescribing and taking medicines. British Medical Journal 2003;327:819-20.

144. Charles C, Whelan T, Gafni A. What do we mean by partnership in making decisions about treatment? British Medical Journal 1999;319:780-2.

145. Thomson R, Bowling A, Moss F. Engaging patients in decisions: a challenge to health care delivery and public health. Quality in Health Care 2001;10(Suppl I):i1.

146. Meryn S. Improving doctor-patient communication: not an option, but a necessity. British Medical Journal 1998;316:1922.

147. Little P, Everitt H, Williamson I, Warner G, Moore M, Gould C et al. Preferences of patients for patient-centred approach to consultation in primary care. British Medical Journal 2001;322:468-72.

148. Little P, Everitt H, Williamson I, Warner G, Moore M, Gould C et al. Observational study of effect of patient centredness and positive approach on outcomes of general practice consultations. British Medical Journal 2001;323:908-11.

149. Donovan JL. Patient decision making: the missing ingredient in compliance research. International Journal of Technology Assessment in Health Care 1995;11(3):443-55.

150. Dickinson D, Raynor DKT. Ask the patients - they may want to know more than you think. British Medical Journal 2003;327:861-4.

151. Elwyn G, Edwards A, Kinnersley P. Shared decision-making in primary care: the neglected second half of the consultation . British Journal of General Practice 1999;49(477):482.

152. Charles C, Gafni A, Whelan T. Shared decision-making in the medical encounter: what does it mean (or it takes at least two to tango). Social Science & Medicine 1997;44:681-92.

153. Stevenson FA, Barry CA, Britten N, Barber N, Bradley CP. Doctor-patient communication about drugs: the evidence for shared decision making. Social Science & Medicine 2000;50(6):829-40.

154. Britten N, Stevenson FA, Barry CA, Barber N, Bradley CP. Misunderstandings in prescribing decisions in general practice: qualitative study. British Medical Journal 2000;320:484-8.

155. Edwards A, Elwyn G. Understanding risk and lessons for clinical risk communication about treatment preferences. Quality in Health Care 2001;10(Suppl I):i9-i13.

156. Lloyd AJ. The extent of patients' understanding of the risk of treatments. Quality in Health Care 2001;10(Suppl I):i14-i18.

157. Council of the European Communities. European Commission Council Directive. Brussels: European Commission; 2003.

158. Misselbrook D, Armstrong D. Patients' responses to risk information about the benefits of treating hypertension. British Journal of General Practice 2001;51(465):276-9.

159. O'Connor AM, Stacey D, Rovner D, Holmes-Rovner M, Tetroe J, Llewellyn-Thomas H et al. Decision aids for people facing health treatment or screening decision (Cochrane Review). Issue 4, 1st ed. Oxford: Update Software; 2003.

160. Montgomery AA, Fahey T. How do patients' treatment preferences compare with those of clinicians? Quality in Health Care 2001(Suppl I): i39-i43.

161. McAlister FA, Levine M, Zarnke KB, Campbell N, Lewanczuk R, Leenen F et al. The 2000 Canadian recommendations for the management of hypertension: Part one - Therapy. Canadian Journal of Cardiology 2001;17(5):543-59.

162. Montgomery AA, Harding J, Fahey T. Shared decision making in hypertension: The impact of patient preferences on treatment choice. Family Practice 2001;18(3):309-13.

163. Elwyn G, Edwards A, Mowle S, Wensing M, Wilkinson C, Kinnersley P et al. Measuring the involvement of patients in shared decision making: a systematic review of instruments. Patient Education and Counselling 2001;43:5-22.

164. Lewin SA, Skea ZC, Entwistle V, Zwarenstein M, Dick J. Interventions to promote a patient-centred approach to clinical consultations (Cochrane Review). Oxford: Update Software; 2003.

165. Eastabrooks C, Goel V, Thiel E, Pinfold P, Sawka C, Williams I. Decision aids: are they worth it? A systematic review. Journal of Human Hypertension 2001;6(3):170-82.

166. Dowell J, Hudson H. A qualitative study of medication-taking behaviour in primary care. Family Practice 1997;14:369-75.

167. Towle A, Godolphin W. Framework for teaching and learning informed decision making. British Medical Journal 1999;319:766-71.

168. Roter DL, Hall JA, Merisca R, Nordstrom B, Cretin D, Svarstad B. Effectiveness of interventions to improve patient compliance: a meta-analysis. Medical Care 1998;36(8):1138-61.

169. Dunbar-Jacob J, Erlen JA, Schlenk E, Ryan C, Sereika S, Doswell W. Adherence in chronic disease. In: Fitzpatrick J, Goeppinger J, editors. Annual Review of Nursing Research. Vol 18. New York : Springer; 2000. p. 48-90.

170. Stanton AL. Determinants of adherence to medical regimens by hypertensive patients. Journal of Behavioral Medicine 1987;10(4):377-94.

171. Benson J, Britten N. Patients' decisions about whether or not to take antihypertensive drugs: qualitative study. British Medical Journal 2002;325:873.

172. Burnier M, Schneider MP, Chiolero A, Stubi CLF, Brunner HR. Electronic compliance monitoring in resistant hypertension: The basis for rational therapeutic decisions. Journal of Hypertension 2001;19(2):335-41.

173. Burnier M, Schneider MP, Chiolero A, Fallab CL, Brunner HR. Objective monitoring of drug compliance: an important step in the management of hypertension resistant to drug therapy. American Journal of Hypertension 1999;12:129A.

174. Bertholet N, Favrat B, Fallab-Stubi C, Brunner H, Burnier M. Why objective monitoring of compliance is important in the management of hypertension. Journal of Clinical Hypertension 2000;2:258-62.

175. The Cochrane Collaboration. Cochrane Reviewers' Handbook. 2002.

176. Egger M, Davey Smith G, Altman D. Systematic reviews in health care: meta-analysis in context. 2ed. London: BMJ Publishing Group; 2001.

177. Dunbar-Jacob J, Dwyer K, Dunning EJ. Compliance with antihypertensive regimen: a review of research in the 1980s. Annals of Behavioral Medicine 1991;13(1):31-9.

178. Morrison A, Wertheimer AI, Berger ML. Interventions to improve antihypertensive drug adherence: A quantitative review of trials. Hospital Formulary 2000;35(3):234-55.

179. Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. British Medical Journal 1994;309:1286-91.

180. Blenkinsopp AP. Extended adherence support by community pharmacists for patients with hypertension: A randomised controlled trial. International Journal of Pharmacy Practice 2000;8(3):165-75.

181. Mehos BM, Saseen JJ, MacLaughlin EJ. Effect of pharmacist intervention and initiation of home blood pressure monitoring in patients with uncontrolled hypertension. Pharmacotherapy 2000;20(11 I):1384-9.

182. Andrejak M, Genes N, Vaur L, Poncelet P , Clerson P, Carre A. Electronic pill-boxes in the evaluation of antihypertensive treatment compliance: Comparison of once daily versus twice daily regimen. American Journal of Hypertension 2000;13(2):184-90.

183. Asplund J, Danielson M, Ohman P. Patients compliance in hypertension-the importance of number of tablets. British Journal of Clinical Pharmacology 1984;17(5):547-52.

184. Baird MG, Bentley-Taylor MM, Carruthers SG, Dawson KG, Laplante LE, Larochelle P et al. A study of efficacy, tolerance and compliance of once-daily versus twice daily metoprolol (Betaloc) in hypertension. Clinical & Investigative Medicine 1984;7:95-102.

185. Burris JF, Papademetriou V, Wallin JD, Cook ME, Weidler DJ. Therapeutic adherence in the elderly: transdermal clonidine compared to oral verapamil for hypertension. American Journal of Medicine 1991;91(Suppl. 1A):22S-8S.

186. Detry J-M, Block P, De Backer G, Degaute J-P. Patient compliance and therapeutic coverage: comparison of amlodipine and slow release nifedipine in the treatment of hypertension. European Journal of Clinical Pharmacology 1995;47:477-81.

187. Boissell JP, Meillard O, Perrin-Fayolle E, Ducruet T, Alamercery Y, Sassano P et al. Comparison between a bid and tid regimen: improved compliance with no

improved antihypertensive effect. European Journal of Clinical Pharmacology 1996;50(1-2):63-7.

188. Leenen FH, Wilson TW, Bolli P, Larochelle P, Myers M, Handa SP et al. Patterns of compliance with once versus twice daily antihypertensive drug therapy in primary care: a randomized clinical trial using electronic monitoring. Canadian Journal of Cardiology 1997;13(10):914-20.

189. Mounier-Vehier C, Bernard C, Carre A, Lequeuche B, Hotton J-M, Charpentier J-C. Compliance and antihypertensive efficacy of amlodipine compared with nifedipine slow-release. American Journal of Hypertension 1998;11:478-86.

190. Girvin B, McDermott BJ, Johnston GD. A comparison of enalapril 20 mg once daily versus 10 mg twice daily in terms of blood pressure lowering and patient compliance. Journal of Hypertension 1999;17(11):1627-31.

191. Webb PA. Effectiveness of patient education and psychosocial counseling in promoting compliance and control among hypertensive patients. Journal of Family Practice 1980;10(6):1047-55.

192. Kirscht JP, Kirscht JL, Rosenstock IM. A test of interventions to increase adherence to hypertensive medical regimens. Health Education Quarterly 1981;8(3):261-72.

193. Pierce JP, Watson DS, Knights S, Gliddon T, Williams S, Watson R. A controlled trial of health education in the physician's office. Preventive Medicine 1984;13(2):185-94.

194. Kerr JAC. Adherence and self-care. Heart and Lung 1985;14(1):24-31.

195. Marquez-Contreras E, Casado-Martinez JJ, Ramos-Perez J, Saenz-Soubrier S, Moreno-Garcia JP, Celotti-Gomez B et al. Trial on the efficacy of programmes of health education on hypertension therapy compliance. Atencion-Primaria 1998;21 (4):199-204.

196. Eshelman FN, Fitzloff J. Effect of packaging on patient compliance with an antihypertensive medication. Current Therapeutic Research, Clinical & Experimental 1976;20(2):215-9.

197. Gabriel M, Gagnon JP, Bryan CK. Improved patients compliance through use of a daily drug reminder chart. American Journal of Public Health 1977;67:968-9.

198. Johnson AL, Taylor DW, Sackett DL, Dunnett CW, Shimizu AG. Self-recording of blood pressure in the management of hypertension. Canadian Medical Association Journal 1978;119(9):1034-9.

199. Nessman DG, Carnahan JE, Nugent CA. Increasing compliance. Patient-operated hypertension groups. Archives of Internal Medicine 1980;140(11):1427-30.

200. Becker LA, Glanz K, Sobel E, Mossey J, Zinn SL, Knott KA. A randomized trial of special packaging of antihypertensive medications. Journal of Family Practice 1986;22(4):357-61.

201. Burrelle TN. Evaluation of an interdisciplinary compliance service for elderly hypertensives. J Geriatr Drug Ther 1986;1(2):23-51.

202. Friedman RH, Kazis LE, Jette A, Smith MB, Stollerman J, Torgerson J et al. A telecommunications system for monitoring and counseling patients with hypertension. Impact on medication adherence and blood pressure control. American Journal of Hypertension 1996;9(4 Pt 1):285-92.

203. Hamilton GA, Roberts SJ, Johnson JM, Tropp JR, Anthony-Odgren D, Johnson BF. Increasing adherence in patients with primary hypertension: an intervention. Health Values 1993;17(1):3-11.

204. Hawkins DW, Fiedler FP, Douglas HL. Evaluation of a clinical pharmacist in caring for hypertensive and diabetic patients. American Journal of Hospital Pharmacy 1979;36(10):1321-5.

205. Haynes RB, Sackett DL, Gibson ES, Taylor DW, Hackett BC, Roberts RS et al. Improvement of medication compliance in uncontrolled hypertension. Lancet 1976;1(7972):1265-8.

206. Logan AG, Milne BJ, Achber C, Campbell WP, Haynes RB. Work-site treatment of hypertension by specially trained nurses. A controlled trial. Lancet 1979;2(8153):1175-8.

207. Logan AG, Milne BJ, Flanagan PT, Haynes RB. Clinical effectiveness and cost-effectiveness of monitoring blood pressure of hypertensive employees at work. Hypertension 1983;5(6):828-36.

208. McKenney JM, Munroe WP, Wright JT, Jr. Impact of an electronic medication compliance aid on long-term blood pressure control. Journal of Clinical Pharmacology 1992;32(3):277-83.

209. Morisky DE, DeMuth NM, Field-Fass M, Green LW, Levine DM. Evaluation of family health education to build social support for long-term control of high blood pressure. Health Education Quarterly 1985;12(1):35-50.

210. Park JJ, Kelly P, Carter BL, Burgess PP . Comprehensive pharmaceutical care in the chain setting . Journal of the American Pharmaceutical Association 1996;NS36(7):443-51.

211. Rehder TL, McCoy LK, Blackwell B, Whitehead W, Robinson A. Improving medication compliance by counseling and special prescription container. American Journal of Hospital Pharmacy 1980;37(3):379-85.

212. Saunders LD, Irwig LM, Gear JS, Ramushu DL. A randomized controlled trial of compliance improving strategies in Soweto hypertensives. Medical Care 1991;29(7):669-78.

213. Sclar DA, Chin A, Skaer TL, Okamoto MP, Nakahiro RK, Gill MA. Effect of health education in promoting prescription refill compliance among patients with hypertension. Clinical Therapeutics 1991;13(4):489-95.

214. Skaer TL, Sclar DA, Markowski DJ, Won JKH. Effect of value-added utilities in promoting prescription refill compliance among patients with hypertension. Current Therapeutic Research 1993;53:251.

215. Solomon DK, Portner TS, Bass GE, Gourley DR, Gourley GA, Holt JM et al. Clinical and economic outcomes in the hypertension and COPD arms of a multicenter outcomes study. Journal of the American Pharmaceutical Association 1998;38(5):574-85.

216. Zarnke KB, Feagan BG, Mahon JL, Feldman RD. A randomized study comparing a patient-directed hypertension management strategy with usual office-based care. American Journal of Hypertension 1997;10(1):58-67.

217. Bowling A, Ebrahim S. Measuring patients' preferences for treatment and perceptions of risk. Quality in Health Care 2001;10(Suppl I):i2-i8.

218. Sieber WJ, Kaplan RM. Informed adherence: the need for shared medical decision making. Controlled Clinical Trials 2000;21:233S-40S.

219. Rand C, Sevick MA. Ethics in adherence promoting and monitoring. Controlled Clinical Trials 2000;21:241S-7S.

220. Montgomery AA, Fahey T, Peters TJ, MacKintosh C, Sharp D. Evaluation of a computer-based clinical decision support system and chart guidelines in the management of hypertension in primary care: a randomised controlled trial. British Medical Journal 2000;320:686-90.

221. Nessman DG, Carnahan JE, Nugent CA. Increasing compliance. Patient-operated hypertension groups. Archives of Internal Medicine 1980;140(11):1427-30.

222. Medical Research Council. Primary Health Care: Topic Review. London: Medical Research Council; 1997.

223. Department of Health. R&D in Primary Care: National Working Group Report. London: The Stationery Office; 1997.

224. Thomas T, Fahey T, Somerset M. The content and methodology of research papers published in three United Kingdom primary care journals. British Journal of General Practice 1998;48:1229-32.

225. Collins R, Peto R, MacMahon S, Hebert P, Fiebach N, Eberlein KA et al. Blood pressure, stroke and coronary heart disease. Part 2, short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. Lancet 1990;335:827-38.

226. Montgomery A, Fahey T, Peters TJ. A factorial randomised controlled trial of decision analysis and an information video plus leaflet for newly diagnosed hypertensive patients. British Journal of General Practice 2003;53:446-53.

227. Kessel A. Ethics and research in psychiatry. International Review of Psychiatry 1998;10:331-7.

228. Beauchamp TL, Childress JF. Principles of biomedical ethics. 4thed. New York: Oxford University Press; 1994.

229. Medical Research Council. MRC guidelines for good clinical practice in clinical trials. Mitcham, Surrey: Medical Research Council Publications Department; 1998.

230. Moher D, Schulz KF, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized controlled trials. Journal of the American Medical Association 2001;285(15):1987-91.

231. Bristol South & West Primary Care Trust and United Bristol Healthcare Trust. Guidance on prescribing for hypertension, angina and heart failure. Bristol: Bristol South & West Primary Care Trust and United Bristol Healthcare Trust; 2002.

232. Rejeski WJ, Brawley LR, McAuley E, Rapp S. An examination of theory and behavior change in randomized controlled trials. Controlled Clinical Trials 2000;21:164S-70S.

233. Campbell M, Fitzpatrick R, Haines A, Kinmonth AL, Sandercock P, Spiegelhalter D et al. Framework for design and evaluation of complex interventions to improve health. British Medical Journal 2000;321:694-6.

234. Wolff N. Randomised trials of socially complex interventions: promise or peril? Journal of Health Services Research & Policy 2001;6(21):123-6.

235. Maguire P, Pitceathly C. Key communication skills and how to acquire them. British Medical Journal 2002;325:697-700.

236. Charles C, Whelan T, Gafni A. What do we mean by partnership in making decisions about treatment? British Medical Journal 1999;319:780-2.

237. Charles C, Gafni A, Whelan T. Decision-making in the physician-patient encounter: revisiting the shared treatment decision making model. Social Science & Medicine 1999;49:651-61.

238. Steele DJ, Jackson TC, Gutmann MC. Have you been taking your pills? The Journal of Family Practice 1989;30(3):294-9.

239. Roberts C, Torgerson D. Randomisation methods in controlled trials. British Medical Journal 1998;317:1301.

240. Altman DG, Schulz KF. Concealing treatment allocation in randomised trials. British Medical Journal 2001;323:446-7.

241. Stata Corporation. Stata Statistical Software: Release 8.0. College Station, TX: Stata Corporation; 2003.

242. Strobl J, Cave E, Walley T. Data protection legislation: interpretation and barriers to research. British Medical Journal 2000;321:890-2.

243. Roland M, Torgerson D. What outcomes should be measured? British Medical Journal 1998;317:1075.

244. Peto R, Collins R, Gray R. Large scale randomised evidence: large simple trials and overviews of trials. Journal of Clinical Epidemiology 1995;48(23):40.

245. Levine RA. Monitoring for adherence: ethical considerations. American Journal of Respiratory Critical Care Medicine 1994;149:287-8.

246. Rand CS, Wise RA, Nides M, Simmons MS, Bleeker ER, Kusek JW et al. Metered-dose inhaler adherence in a clinical trial. American Review of Respiratory Disease 1992;146:1559-64.

247. Cramer JA, Ouelette VL, Mattson RH. The effect of microelectronic observation on compliance. Epilepsia 1990;31:617-8.

248. Rand CS, Sevick MA. Ethics in adherence promotion and monitoring. Controlled Clinical Trials 2000;21:241S-7S.

249. Britten N. Commentary: Does a prescribed treatment match a patient's priorities. British Medical Journal 2003;327:840.

250. McAlister FA, Straus SE. Measurement of blood pressure: an evidence based review. British Medical Journal 2001;322:908-11.

251. O'Brien E, Waeber B, Parati G, Staessen J, Myers MG. Blood pressure measuring devices: recommendations of the European Society of Hypertension. British Medical Journal 2001;322:531-6.

252. Fergusson D, Aaron SD, Guyatt G, Hebert P. Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. British Medical Journal 2002;325:652-4.

253. Vickers A, Altman D. Analysing controlled trials with baseline and follow up measurements. British Medical Journal 2001;323:1123-4.

254. Brookes S, Peters TJ, Whitley E, Davey Smith G, Mulheran PA, Egger M. Subgroup analyses in randomized controlled trials: risks of subgroup-specific analyses; power and sample size for the interaction test. Journal of Clinical Epidemiology 2003;in press.

255. Park L, Lipman RS. A comparison of patient dosage deviation reports with pill counts. Psychopharmacologia 1964;6:299-302.

256. Rickels K, Briscoe E. Assessment of dosage deviation in outpatient drug research. Journal of Clinical Pharmacology 1970;10:153-60.

257. George CF, Peveler RC, Heiliger S, Thompson C. Compliance with tricyclic antidepressants: the value of four different methods of assessment. British Journal of Clnical Pharmacology 2000;50:166-71.

258. Stone VE, Hogan JW, Schuman P, Rompalo AM, Howard AA, Korkontzelou C et al. Antiretroviral regimen complexity, self-reported adherence, and HIV

patients' understanding of their regimens: Survey of women in the HER study. Journal of Acquired Immune Deficiency Syndromes 2001;28(2):124-31.

259. Ogedegbe G, Manusco CA, Allegrante JP, Charlson ME. Development and evaluation of a medication adherence self-efficacy scale in hypertensive African-American patients. Journal of Clinical Epidemiology 2003;56:520-9.

260. Inui TS, Carter WB, Pecoraro RE. Screening for noncompliance among patients with hypertension: is self-report the best available measure? Medical Care 1981;19(10):1061-4.

261. Stewart M. The validity of an interview to assess a patient's drug taking. American Journal of Preventive Medicine 1987;3:95-100.

262. Gordis L, Markowitz M, Lilienfeld AM. The inaccuracy of using interviews to estimate patient reliability in taking medications at home. Medical Care 1969;7:49-54.

263. Craig HM. Accuracy of indirect measures of medication compliance in hypertension. Research in Nursing & Health 1985;8 (1):61-6.

264. de Klerk E, van der Heijde D, van der Tempel H, van der Linden S. Development of a questionnaire to investigate patient compliance with antirheumatic drug therapy. Journal of Rheumatology 1999;25:2635-41.

265. Bowling A. Research Methods in Health: investigating health and health services. Buckingham: Open University Press; 1997.

266. Urquhart J. Defining the margins for errors in patient compliance with prescribed drug regimens. Pharmacoepidemiology & Drug Safety 2000;9(7):565-8.

267. Buchan J. Global nursing shortages. British Medical Journal 2002;324:751-2.

268. Finlayson B, Dixon J, Meadows S, Blair G. Mind the gap: the extent of the NHS nursing shortage. British Medical Journal 2002;325:538-41.

269. Gross CP, Mallory R, Heiat A, Krumholz HM. Reporting the recruitment process in clinical trials: who are these patients and how did they get there? Annals of Internal Medicine 2002;137:10-6.

270. Netten A, Curtis L. Unit costs of health and social care 2002. University of Kent: Personal Social Services Research Unit; 2002.

271. Hennekens CH, Buring JE. Epidemiology in medicine. 2nd ed. Boston: Little, Brown; 1987.

272. Detry J-M, Block P, De BG, Degaute J-P, Six R. Patient compliance and therapeutic coverage: Comparison of amlodipine and slow release nifedipine in the treatment of hypertension. European Journal of Clinical Pharmacology 1995;47(6):477-81.

273. Featherstone K, Donovan JL. Random allocation or allocation at random? Patients' perspectives of participation in a randomised controlled trial . British Medical Journal 1998;317:1177-80.

274. Haynes B. Can it work? Does it work? Is it worth it? British Medical Journal 1999;319:652-3.

275. Thomas P. The research needs of primary care. British Medical Journal 2000;321:2-3.

276. Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R. Barriers to participation in randomised controlled trials: a systematic review. Journal of Clinical Epidemiology 1999;52(12):1143-56.

277. Campbell R, Quilty B, Dieppe P. Discrepancies between patients' assessment of outcome: qualitative study nested within a randomised controlled trial. British Medical Journal 2003;326:252-3.

278. Sanders C, Egger M, Donovan J, Tallon D , Frankel S. Reporting on quality of life in randomised controlled trials: bibliographic study. British Medical Journal 1998;317:1197-4.

279. Goodare H, Lockwood S. Involving patients in clinical research. British Medical Journal 1999;319:724-5.

280. Tallon D, Chard J, Dieppe P. Consumer involvement in research is essential. British Medical Journal 2000;320:380.

281. Alderson P. The importance of theories in health care. British Medical Journal 1998;317:1007-10.

Appendices

Appendix 1 In/out sheet used in the systematic review for inclusion or exclusion of titles or abstracts

Interventions used to improve the adherence to treatment in patients with high blood pressure in ambulatory settings

Identification details:

Author:

Year:

Journal Reference:

1. RCT, not before/after or other design?	Y/N
2. Concerned with essential hypertension (not secondary)?	Y/N
3. Ambulatory setting?	Y/N
4. Intervention(s) aimed at improving adherence?	Y/N
5. Outcomes adherence +/- blood pressure?	Y/N

In Out Pending

Appendix 2 Data collection form systematic review

Interventions used to improve the adherence with treatment in patients with high blood pressure

1. IDENTIFICATION DETAILS

Identifier/code for Refman

Name of reviewer

Last name of author and year of publication

Notes and comments on quality of the study

Source of key information (where found, information from unpublished sources and personal communications)

2. VERIFICATION OF STUDY ELIGIBILITY AND METHODS

Type of trial (e.g. parallel or cross-over)

Study duration

Hypothesis (clearly stated a priori?)

Power calculation and outcome that it was based on

2.1. BLINDING TO TREATMENT ALLOCATION (DESCRIPTION)

Patient

Generator

Provider

Outcome assessor

2.2. RANDOMISATION

Randomisation process (yes, no, unclear) and description

2.3. DROPOUTS / LOSS TO FOLLOW-UP

Drop-outs and reasons for drop-out

Loss to follow-up (differentiate between groups)

2.4. COINTERVENTIONS

Cointerventions

Other confounders

3. PARTICIPANTS

Number of participants randomised in each group

Differences in baseline characteristics in intervention and control group

Case definition

Inclusion criteria

Exclusion criteria

Other presenting conditions/Comorbidity

Ethnic origin

Age

Gender

Education/Sociodemography

Setting

Geographical region

4. INTERVENTIONS:

Type and description of interventions

How were interventions delivered?

Intervention in control group

Who delivered interventions?

Time frame / schedule of interventions

Treatment length in total

Duration of follow-up

Type of follow-up

5. OUTCOMES:

Stated primary outcome measures

Reported primary outcome measures

5.1. Blood Pressure

5.1.1. Criterion

5.1.2. How was blood pressure measured?

5.1.3. Baseline blood pressure in intervention group (n=, mean, SD, CI, other)

5.1.4. Baseline blood pressure in control group (n=, mean, SD, CI, other)

5.1.5. Statistical difference between groups

5.1.6. BP at final assessment in intervention group (n=, mean, SD, other)

5.1.7 BP at final assessment in control group (n=, mean, SD, other)

5.1.8. Statistical difference between groups

5.1.9. Reduction in BP in intervention group

5.1.10 Reduction in BP in control group

5.2. Adherence

5.2.1. Criterion

5.2.2. How was adherence measured?

5.2.3. Adherence in intervention group (n=, %)

5.2.4. Adherence in control group (n=, %)

5.2.5. Statistical difference between groups

5.3. Other outcomes

5.3.1. Other outcomes in intervention group

5.3.2. Other outcomes in control group

6. STATISTICS:

Analysis/statistic test used

Intention-to-treat analysis used or not?

7. CONCLUSION:

What conclusion has been reached in the paper?

Does it correspond with the findings?

Appendix 3 Characteristics of RCTs included in systematic review

Study (first author, year of publication)	Study size	Intervention	Control	Method of measuring adherence	Net effect on adherence between intervention and control group (p-value)	Blood pressure change systolic in mmHg (p-value)*	Blood pressure change diastolic in mmHg (p-value)*	Duration of follow-up in months	Comments
Simplification of dosing regimens									
Asplund 1984[183]	160	Pindolol 10mg and clopamide 5mg once daily (single combination tablet)	Pindolol 10mg and clopamide 5mg once daily (separate tablets)	PC, SR	28.2% (NS)	+ 2.8 (NS)	+3 (NS)	4	Bias possible
Baird 1984[184]	389	Once-daily metoprolol 200mg	Twice daily metoprolol 100mg	PC	8% (p=0.009)	1.0 (NS)	0 (NS)	2	Bias possible

Study (first author, year of publication)	Study size	Intervention	Control	Method of measuring adherence	Net effect on adherence between intervention and control group (p-value)	Blood pressure change systolic in mmHg (p-value)*	Blood pressure change diastolic in mmHg (p-value)*	Duration of follow-up in months	Comments
Burris 1991[185]	58	Transdermal clonidine 0.1mg/d plus placebo tablets	Verapamil 120mg slow release tablet plus transdermal placebo	PC, visual assessment	59% (NS)	5 (p<0.05)	1 (p<0.05).	2	Bias possible. Compared two different drugs
Detry 1995[186]	320	Once daily amlodipine 5mg	Twice daily nifedipine 20mg	PC, MEMS®	17.8% (p<0.001)	NS, but no data reported	NS	3	Bias possible. Compared two different drugs
Boissell 1996[187]	7274	Twice daily nicardipine slow release 50mg	Nicardipine 20mg three times a day	SR	11% (p<0.001)	0.2 (NS)	0.3 (NS)	3	Bias possible. Compared two different drugs
Leenen 1997[188]	198	Once daily amlodipine 5mg	Diltiazem slow release 60mg twice daily	MEMS®	8% (p<0.01)	6 (p<0.01)	1 (NS)	5	Compared two different drugs.
Mounier-Vehier 1998[189]	103	Once daily amlodipine 5mg	Twice daily nifedipine 20mg	MEMS®	17.7% (p<0.001)	0.8 mmHg (NS)	+1.1 (NS)	3	Compared two different drugs.

Study (first author, year of publication)	Study size	Intervention	Control	Method of measuring adherence	Net effect on adherence between intervention and control group (p-value)	Blood pressure change systolic in mmHg (p-value)*	Blood pressure change diastolic in mmHg (p-value)*	Duration of follow-up in months	Comments
Girvin 1999[190]	27	Enalapril 20mg once daily	Enalapril 10mg twice daily	MEMS®	19.6% (p<0.001)	5.3 (p=0.068)	1.0 (p=0.086)	3	Potential for selection bias..
Andrejak 2000[182]	162	Once daily trandolapril 2mg	Twice daily captopril 25mg	MEMS®	16% (p<0.001)	14% more with normal blood pressure (NS)	N/A	6	Study compared different drugs.
Patient education									
Sackett 1975[10]	144	Educational programme via slide-audiotape and booklet	Usual care	PC	5% (NS)	24% at goal bp and compliant in intervention group versus 19% in control group (NS)	NR	6	Well-designed study

Study (first author, year of publication)	Study size	Intervention	Control	Method of measuring adherence	Net effect on adherence between intervention and control group (p-value)	Blood pressure change systolic in mmHg (p-value)*	Blood pressure change diastolic in mmHg (p-value)*	Duration of follow-up in months	Comments
Webb 1980[191]	92	Group education	Regular physician appointments	PC	Compliance score 0.2 points higher (p>0.10)	NR	3.3 (p>0.1)	3	Randomisation process and blinding to outcome assessment not reported.
Kirscht 1981[192]	343	Written educational material	Usual care	SR	1% (NS)	NR	NR	18	Adherence scores unclear and difficult to interpret.
Pierce 1984[193]	29	Health education in groups, four meetings of 90 minutes duration	Usual care	PC, SR	4% more 'good' adherers (NS)	16% more patients had blood pressure reduction (p<0.05, effect size unclear)	N/A	6	Outcomes inadequately reported

Study (first author, year of publication)	Study size	Intervention	Control	Method of measuring adherence	Net effect on adherence between intervention and control group (p-value)	Blood pressure change systolic in mmHg (p-value)*	Blood pressure change diastolic in mmHg (p-value)*	Duration of follow-up in months	Comments
Kerr 1985[194]	60	Education via visual aids and 10-minute lecture, followed by discussion and knowledge test	No intervention apart from paper and pencil tests	SR	12.5% (NS)	NR	4.6 (NS)	3	Large dropouts and inconsistencies between text and tables.
Márquez Contreras 1998[195]	110	Group education in groups of 15 over 90 minutes and postal information leaflets at 1, 3 and 5 months	Usual care	PC	24% (p<0.002)	NR	NR	6	Unclear how dropouts were treated.
Patient motivation, support and reminders									

Study (first author, year of publication)	Study size	Intervention	Control	Method of measuring adherence	Net effect on adherence between intervention and control group (p-value)	Blood pressure change systolic in mmHg (p-value)*	Blood pressure change diastolic in mmHg (p-value)*	Duration of follow-up in months	Comments
Eshelman 1976[196]	100	Compliance dispenser	Usual medicine bottle	PC, DQ	2% (NS)	NR	NR	NR	Drop-outs at least 33%.
Gabriel 1977[197]	79	Daily drug reminder chart with pharmacist supervision	No chart (i.e. usual care)	PC, DQ	12% (p=0.002)	NR	NR	3 ½	Small study, no power calculation reported, unreliable assessment of adherence.
Johnson 1978[198]	68	Self-recording of blood pressure	Usual care	PC	12% (NS)	2 (NS)	NR	6	Study likely to be underpowered
Johnson 1978[198]	67	Monthly home visits	Usual care	PC, SR	10% (NS)	2 (NS)	NR	6	Power calculation not reported, study likely to be underpowered

Study (first author, year of publication)	Study size	Intervention	Control	Method of measuring adherence	Net effect on adherence between intervention and control group (p-value)	Blood pressure change systolic in mmHg (p-value)*	Blood pressure change diastolic in mmHg (p-value)*	Duration of follow-up in months	Comments
Nessman 1980[199]	52	Nurse and psychologist teaching self-determination, eight weekly training sessions lasting 90 minutes	Nurse and protocol-run clinic	PC	Intervention group compliant for 1.3 more weeks than the control group (p<0.001)	6 (p<0.05)	NR	2	Only 10% of eligible patients took part in the study with potential selection bias. Other potential sources of bias poorly reported.
Rehder 1980[211]	50	Counselling (instructions on medication-taking, information giving and discussion of side effects)	Usual care	PC	2% (NS)	NR	9 (NS)	6	High drop-out rate, study underpowered. Results poorly reported.
Rehder 1980[211]	50	Special medication container	Usual medication vials	PC	6%(NS)	1 (NS)	NR	6	High drop-out rate, study underpowered. Results poorly reported.

Study (first author, year of publication)	Study size	Intervention	Control	Method of measuring adherence	Net effect on adherence between intervention and control group (p-value)	Blood pressure change systolic in mmHg (p-value)*	Blood pressure change diastolic in mmHg (p-value)*	Duration of follow-up in months	Comments
Webb 1980[191]	86	Counselling (three sessions with trained social worker, lasting one hour each at three weekly intervals)	Regular physician appointments	Pill count	0.2 points difference in adherence score between baseline and follow-up (p>0.10)	NR	2.3 (p>0.1)	18	Randomisation process and blinding to outcome assessment not reported.
Kirscht 1981[192]	316	Nurse phone calls	Usual care	SR	5% (p<0.05)	NR	NR	18	Adherence scores unclear and difficult to interpret.
Kirscht 1981[192]	203	Self-recording of blood pressure	Usual care	SR	0% (NS)	NR	NR	18	Adherence scores unclear and difficult to interpret.
Kirscht 1981[192]	228	Social support	Usual care	SR	5% (p<0.05)	NR	NR	N/A	Adherence scores unclear and difficult to interpret. Exact nature of intervention unclear.

Study (first author, year of publication)	Study size	Intervention	Control	Method of measuring adherence	Net effect on adherence between intervention and control group (p-value)	Blood pressure change systolic in mmHg (p-value)*	Blood pressure change diastolic in mmHg (p-value)*	Duration of follow-up in months	Comments
Pierce 1984[193]	27	Self monitoring of blood pressure	Usual care	PC, SR	6% (NS)	4% more participants had blood pressure reduction (NS)	NR	6	Randomisation procedure prone to bias. Reporting of outcomes inadequate
Kerr 1985[194]	59	Teaching session on how to take and record own blood pressure	No intervention apart from paper and pencil tests	SR	4% (NS)	NR	+0.4 NS	3	Large dropouts and inconsistencies between text and tables.
Morisky 1985[209]	66	Family member support through training by health educator	Usual care by physician	SR	13% (p<0.05)	25% more participants controlled (p<0.05)	NR	60	Randomisation method not reported, complex design

Study (first author, year of publication)	Study size	Intervention	Control	Method of measuring adherence	Net effect on adherence between intervention and control group (p-value)	Blood pressure change systolic in mmHg (p-value)*	Blood pressure change diastolic in mmHg (p-value)*	Duration of follow-up in months	Comments
Morisky 1985[209]	65	Counselling session with health educator directly after doctor appointment (10 min)	Usual care by physician	SR	4% (NS)	4% more participants controlled (NS)	NR	60	Randomisation method not reported, complex design.
Morisky 1985[209]	62	Small group training groups	Usual care by physician	SR	0% (NS)	4% more participants controlled (NS)	No	60	Randomisation method not reported, complex design.
Becker 1986[200]	180	Special unit-dose reminder packaging	No intervention	PC, SR	9% (NS)	NR	0.2 (NS)	12	Randomisation procedure not reported. Participating physicians blind to treatment allocation.

Study (first author, year of publication)	Study size	Intervention	Control	Method of measuring adherence	Net effect on adherence between intervention and control group (p-value)	Blood pressure change systolic in mmHg (p-value)*	Blood pressure change diastolic in mmHg (p-value)*	Duration of follow-up in months	Comments
McKenney 1992[208]	70	Electronic medication aid cap	Usual drug vial	PC	17% (p=0.0002)	NR	NR	3	Small sample size, potential sources of bias poorly reported.
Skaer 1993[214]	151	Postal reminder	Usual care	Prescription record	8% (p<0.05)	NR	NR	12	Sources of bias not fully reported.
Skaer 1993[214]		Special unit-dose reminder packaging	Usual care	Prescription record	11% (p<0.05)	NR	NR	12	Sources of bias not fully reported.
Skaer 1993[214]		Postal reminder combined with special unit-dose reminder packaging	Usual care	Prescription record	23% (p<0.05)	NR	NR	12	Sources of bias not fully reported.
Friedman 1996[202]	267	Telephone-linked computer counselling	Usual care	PC	6% (p=0.03)	4.7 (p=0.85))	4.4 (p=0.09	6	Treatment provided blinded until baseline measurements completed.

Study (first author, year of publication)	Study size	Intervention	Control	Method of measuring adherence	Net effect on adherence between intervention and control group (p-value)	Blood pressure change systolic in mmHg (p-value)*	Blood pressure change diastolic in mmHg (p-value)*	Duration of follow-up in months	Comments
Park 1996[210]	64	Pharmacy-based education and counselling	Traditional pharmacy services	PC	-2.3% (NS)	NR	NR	4	Small sample size, method of randomisation not reported.
Zarnke 1997[216]	31	Home blood pressure monitoring and self-management	Usual care	PC (not clearly defined)	0.2 less doses missed (NS)	2.9 (mean arterial blood pressure, p=0.039)	NR	2	Small sample size.
Complex health and organisational interventions, interventions in combination									

Study (first author, year of publication)	Study size	Intervention	Control	Method of measuring adherence	Net effect on adherence between intervention and control group (p-value)	Blood pressure change systolic in mmHg (p-value)*	Blood pressure change diastolic in mmHg (p-value)*	Duration of follow-up in months	Comments
Sackett 1975[10]	144	Physician-led work site care (augmented convenience)	Usual care	PC	3% (NS)	4% more compliant and at goal blood pressure (NS)	NR	6	Randomisation process not reported. Outcome assessors were blinded to treatment allocation.
Haynes 1976[205]	39	Self-measurement of blood pressure, medication and blood pressure charting, tailoring to daily routines, fortnightly review and rewards (financial and praise)	Usual care	PC	23% (p<0.025)	NR	4 (p=0.12)	6	Potential sources of bias well reported. Study underpowered to detect effect on blood pressure.

Study (first author, year of publication)	Study size	Intervention	Control	Method of measuring adherence	Net effect on adherence between intervention and control group (p-value)	Blood pressure change systolic in mmHg (p-value)*	Blood pressure change diastolic in mmHg (p-value)*	Duration of follow-up in months	Comments
Johnson 1978[198]	69	Self-recording of blood pressure and monthly home visits	Usual care	PC, SR	10% (NS)	1 (NS)	NR	6	Power calculation not reported, study likely to be underpowered.
Hawkins 1979[204]	1148	Post-diagnostic management of patients with hypertension and diabetes by clinical pharmacist	Usual physician review	Prescribing record	Diuretic only: 7.6% (p<0.7) Diuretic plus methyldopa: 19.2% (p=0.2)	4 (p<0.001)	0 (NS)	29	High losses to follow-up (45%).
Logan 1979[206]	457	Work-site management of hypertension by specially trained nurses	Usual care	PC	18% (p<0.005)	NR	4 (p<0.001)	6	Randomisation process not stated.

Study (first author, year of publication)	Study size	Intervention	Control	Method of measuring adherence	Net effect on adherence between intervention and control group (p-value)	Blood pressure change systolic in mmHg (p-value)*	Blood pressure change diastolic in mmHg (p-value)*	Duration of follow-up in months	Comments
Rehder 1980[211]	50	Counselling and special medication container	Usual medication vials	PC	11% NS	NR	18 (p<0.02)	6	High drop-out rate, study underpowered. Results poorly reported.
Logan 1983[207]	194	Structured hypertension management by occupational health nurses	Usual care	PC	+1% (NS)	NR	3 (NS)	12	Randomisation process unclear.
Pierce 1984[193]	30	Self monitoring of blood pressure and health education	Usual care	PC, SR	2% (NS))	4% more had blood pressure reduction (NS)	NR	6	Randomisation procedure prone to bias. Outcome assessor blind to treatment allocation. Reporting of outcomes inadequate.

Study (first author, year of publication)	Study size	Intervention	Control	Method of measuring adherence	Net effect on adherence between intervention and control group (p-value)	Blood pressure change systolic in mmHg (p-value)*	Blood pressure change diastolic in mmHg (p-value)*	Duration of follow-up in months	Comments
Kerr 1985[194]	116	Education through visual aids and 10-minute lecture plus self-monitoring	No intervention apart from paper and pencil tests	SR	+2% (NS)	+1 (NS)	NR	3	Large dropouts and inconsistencies between text and tables.
Morisky 1985[209]	72	Education, family member support and small training groups	Usual care by physician	SR	5% (NS)	29% more participants controlled (p<0.01)	NR	60	Randomisation method not reported, complex design
Burrelle 1986[201]	16	Home visits, education and special dosing devices	Usual care	PC, SR	21% (p<0.001)	7 (p>0.05)	+7 (p>0.05)	2	Small study. High likelihood of bias.

Study (first author, year of publication)	Study size	Intervention	Control	Method of measuring adherence	Net effect on adherence between intervention and control group (p-value)	Blood pressure change systolic in mmHg (p-value)*	Blood pressure change diastolic in mmHg (p-value)*	Duration of follow-up in months	Comments
Saunders 1991 [212]	115	Written reminders, patient-held records and home visits (newly diagnosed)	Usual care	PC	16% (p=0.19)	NR	7 (NS)	6	Randomisation method not reported. Data on adherence only in 40% of participants.
Saunders 1991[212]	109	Written reminders, patient-held records and home visits (infrequent attenders)	Usual care	PC	31% (p=0.009)	+4.3 (NS)	NR	6	Randomisation method not reported. Data on adherence only in 66% of participants.

Study (first author, year of publication)	Study size	Intervention	Control	Method of measuring adherence	Net effect on adherence between intervention and control group (p-value)	Blood pressure change systolic in mmHg (p-value)*	Blood pressure change diastolic in mmHg (p-value)*	Duration of follow-up in months	Comments
Sclar 1991[213]	344	Educational leaflet, telephone reminder, mailed reminder and educational newsletter (previously treated)	Usual care	PC	'Medication possession ratio' 34% higher ($p<0.05$)	NR	NR	6	Potential sources of bias poorly reported.
Sclar 1991[213]	109	Educational leaflet, telephone reminder, mailed reminder and educational newsletter (newly diagnosed)	Usual care	PC	'Medication possession ratio' 41% higher ($p<0.05$)	NR	NR	6	Potential sources of bias poorly reported.

Study (first author, year of publication)	Study size	Intervention	Control	Method of measuring adherence	Net effect on adherence between intervention and control group (p-value)	Blood pressure change systolic in mmHg (p-value)*	Blood pressure change diastolic in mmHg (p-value)*	Duration of follow-up in months	Comments
Hamilton 1993[203]	34	Postcard reminder, nurse-led educational appointment and follow-up phone call	Usual care	SR	3 points difference in adherence score (p=0.12)	17.3 (p=0.03)	4.7 (p=0.22)	6	Small study, randomisation method not reported.
Solomon 1998[215]	133	Patient-centred pharmaceutical care model by pharmacy residents	Usual care	PC	0.3 points difference in adherence score (p<0.05)	6.9 (p<0.05)	0.6 (NS)	6	Only results from self-report of adherence reported. High likelihood of bias.

Study (first author, year of publication)	Study size	Intervention	Control	Method of measuring adherence	Net effect on adherence between intervention and control group (p-value)	Blood pressure change systolic in mmHg (p-value)*	Blood pressure change diastolic in mmHg (p-value)*	Duration of follow-up in months	Comments
Blenkinsopp 2000[180]	180	Structured, brief questioning protocol on medication problems; including advice, information and referral to general practitioner by pharmacists three times at two-month intervals	Usual care, delivered three times at two-month intervals	SR	12% (p<0.05)	18.6% more participants controlled (p<0.05)	NR	6	Complete data on blood pressure only available on 100 participants. High likelihood of bias.

Study (first author, year of publication)	Study size	Intervention	Control	Method of measuring adherence	Net effect on adherence between intervention and control group (p-value)	Blood pressure change systolic in mmHg (p-value)*	Blood pressure change diastolic in mmHg (p-value)*	Duration of follow-up in months	Comments
Mehos 2000[181]	41	Home blood pressure monitoring, diary, instruction to measure blood pressure, information on hypertension and risk factors with subsequent evaluation by clinical pharmacist	Usual care	Prescription refill data	+7% (p=0.29)	10.1 (p=0.069)	6.7 (p=0.02)	6	Patients randomised using a 'deck of cards'.

MEMS® = medication event monitoring system
* Net blood pressure reduction from baseline to follow-up in the intervention group compared to controls or percentage of participants with controlled blood pressure
PC = pill counts
DQ = direct questioning
SR = self report
NS = not significant (used when no p-value was reported)

Appendix 4 Quality assessment of included trials for the systematic review and potential sources of bias

	Randomisation procedure appropriate?	Outcome assessor blind to treatment allocation?	Losses to follow-up No (%)	Power calculation reported?	Hypothesis stated a priori?	Comments concerning the validity of the study results
Sackett 1975	NR	yes	10/144 (6.9)	NR	yes	No power calculation as such, but important differences a priori reported
Eshelman 1976	NR	NR	33/100 (33.0)	no	no	Drop-outs at least 33% with no differential loss to follow-up reported.
Haynes 1976	yes	yes	5/39 (12.8)	yes	yes	Lacked statistical power. Power calculation was performed, but no exact figures were reported.
Gabriel 1977	NR	NR	0/79 (0)	no	yes	No power calculation performed
Johnson 1978	NR	yes	4/140 (2.9)	(yes)	yes	Power calculation not reported in methods, but probability of type II error quantified in discussion
Hawkins 1979	yes	no	519/1148 (45.2)	no	yes	High losses to follow-up.
Logan 1979	NR	yes	41/457 (9.0)	no	yes	Differential loss to follow-up well reported.
Nessman 1980	NR	no	NR	no	no	Only 10% of eligible patients took part in the study which may indicate self-selection

	Randomisation procedure appropriate?	Outcome assessor blind to treatment allocation?	Losses to follow-up No (%)	Power calculation reported?	Hypothesis stated a priori?	Comments concerning the validity of the study results
Rehder 1980	NR	NR	52/100 (52)	no	no	High drop-out rate and small sample size for a factorial trial.
Webb 1980	NR	NR	NR	yes	no	Unclear on what outcome and treatment difference the power calculation was based on. Unequal numbers due to drop-outs after randomisation but before start of intervention (no reasons given)
Kirscht 1981	NR	NR	66/417 (15.8)	no	no	Adherence scores unclear and results difficult to interpret.
Logan 1983	yes	yes	9/194 (4.6)	yes	yes	Randomisation process unclear.
Asplund 1984	NR	NR	30/160 (18.8)	no	yes	Drop-outs not clearly reported.
Baird 1984	NR	NR	50/289 (17.3)	no	yes	Detailed reasons for loss to follow-up reported
Pierce 1984	yes	yes	2/115 (1.7)	no	no	Outcomes poorly reported
Kerr 1985	NR	NR	52/116 (44.8)	no	yes	Large drop-outs in all groups. Inconsistencies between denominators in tables and drop-outs that vary for blood pressure and adherence outcomes

	Randomisation procedure appropriate?	Outcome assessor blind to treatment allocation?	Losses to follow-up No (%)	Power calculation reported?	Hypothesis stated a priori?	Comments concerning the validity of the study results
Morisky 1985	NR	NR	110/400 (27.5)	no	yes	No significant differences between drop-outs and those who continued to receive care
Becker 1986	NR	NR	15/180 (8.3)	yes	yes	Physicians blinded to treatment allocation. Were aware that compliance study was in progress but unaware of the aims of the study.
Burrelle 1986	NR	NR	0 (0)	no	no	Small study, high likelihood of bias
Burris 1991	yes	yes	9/58 (15.5)	no	yes	No p-values reported for adherence outcome
Saunders 1991	no	yes	33/224 (14.7)	yes	yes	Drop-outs were lower in the intervention groups but much higher in newly treated group than infrequent attenders.
Sclar 1991	NR	NR	NR	no	no	No drop-outs reported despite uneven number randomised.
McKenney 1992	NR	no	NR	no	yes	9 patients required change of medication during second phase, bp measurements were not included in analysis

	Randomisation procedure appropriate?	Outcome assessor blind to treatment allocation?	Losses to follow-up No (%)	Power calculation reported?	Hypothesis stated a priori?	Comments concerning the validity of the study results
Hamilton 1993	NR	NR	4/34 (11.8)	no	yes	Small sample size.
Skaer 1993	yes	yes	NR	No	Yes	Losses to follow-up not reported
Detry 1995	NR	no	18/640 (2.8)	no	no	Cross over RCT, patients double counted
Boissell 1996	yes	no	253/7274 (3.5)	yes	yes	No differential loss to follow-up reported. High participant numbers due to large number of participating general practitioners
Friedman 1996	NR	yes	34/267 (12.7)	no	yes	Treatment provider blinded until baseline measurement was completed. Randomisation by 'paired randomisation protocol'.
Park 1996	NR	no	11/64 (17.2)	yes	yes	Small study.
Leenen 1997	yes	yes	21/198 (10.6)	no	yes	Compared two different drugs. Only within group comparison.
Zarnke 1997	yes	NR	NR	no	yes	No power calculation but primary and secondary hypotheses stated

	Randomisation procedure appropriate?	Outcome assessor blind to treatment allocation?	Losses to follow-up No (%)	Power calculation reported?	Hypothesis stated a priori?	Comments concerning the validity of the study results
Márquez Contreras 1998	NR	NR	15/110 (13.6)	no	yes	Differential loss to follow-up in both treatment arms not reported.
Mounier-Vehier 1998	NR	no	18/103 (17.5)	no	no	Treatment allocation according to 'enrollment order' and 'randomisation list'.
Solomon 1998	NR	no	NR	no	yes	Multiple sources of bias
Girvin 1999	NR	yes	2/27 (7.4)	no		Small study, methods not well reported.
Andrejak 2000	yes	no	29/162 (17.9)	no	yes	Differential loss to follow-up well reported
Blenkinsopp 2000	NR	NR	40/282 (14.2)	no	yes	Randomisation at pharmacy level, complete data on blood pressure only available on 100 patients
Mehos 2000	NR	NR	5/41 (12.2)	no	yes	Inappropriate randomisation method, only single family practice setting, high likelihood of bias.

Appendix 5 Data collection sheets used in the RCT

Appointment check list

Stage	Timing		Procedure	Check
0	After patient consented	Patient invitation	1. Arrange appointment for patient 2. Tell patient to bring in all their medication	
1	Initial visit	All patients	**1. Fill out data collection sheet with patient** **2. Ask patient to fill in self assessment sheet** **3. Label drug containers: patient name, drug dose and frequency** **4. Give out patient information on monitors and go through it with patient (fill in tablet name)** 5. **Arrange an appointment in 2 months time**	
2	2 months after initial visit	Counselling (INTERVENTION GROUP) or bp check (CONTROL GROUP)	**1. Counselling interview INTERVENTION GROUP ONLY) (see separate sheet)** 2. Check blood pressure 3. download electronic monitor	
3	4 months after initial visit	Re-inforcement appointment (INTERVENTION GROUP) or bp check (CONTROL GROUP)	**1. Brief re-inforcement and follow-up interview (INTERVENTION GROUP ONLY) (see separate sheet)** 2. Check blood pressure 3. download monitors	
4	8 months after initial visit	BP check	1. check blood pressure 2. download monitors	
5	14 months after initial visit	BP check	1. Check blood pressure 2. Download monitors	

FIRST PATIENT MEDICATION COUNSELLING SESSION

Patient Name_____**Monitor Number**_____**Study ID**_____**Surgery**_____

This consultation should last no longer than 10 to 20 minutes. It is meant to be a patient-centred approach to deal with any problems in medication-taking in a non-judgemental manner.

Introduction	**Please tick if discussed**
1. Please state that many people find it difficult to take their medication all the time	
2. Explain that reason for appointment is to discuss ANY problems with taking blood pressure tablets	

Assessment of problems with medication taking	**Please circle or tick as appropriate**
Do you ever find it difficult to take your blood pressure tablets?	**Y / N**

If YES to above question, what is the main problem? _____

Problem Category	**Possible question**	**Is this a problem for the patient?**	**Covered during consultation? (please tick)**	**If YES, what solution strategy have you agreed ?**
Side effects	"Do you have any problems with side effects?"	Y / N		(e.g. refer back to GP)
Size or taste of tablets	"Are the size or the taste of the tablets a problem for you?"	Y / N		(e.g. refer back to GP)
Number of doses a day	"Is the number of doses a day a problem for you?"	Y / N		(e.g refer back to GP)
Non-acceptability	"Are you generally happy taking your blood pressure tablets?"	Y / N		(e.g. discuss reasons, negotiation of treatment plan, refer back to GP if necessary)
Forgetfulness	"Do you find it sometimes difficult to remember taking your blood pressure tablets?"	Y / N		(e.g. association of tablet taking with daily activity, family support, modify or simplify treatment, refer back to GP)
Non-comprehension	"Do you know why you are being prescribed blood pressure tablets?"	Y / N		(explanation of diagnosis and risks/benefits of treatment)
Total number of different tablets	"Do you find it difficult for taking many different tablets?"	Y / N		(e.g refer back to GP)
Anything else not covered by the above problem areas (please state)				

TWO MONTH FOLLOW-UP CONSULTATION

*Patient Name*_____*Monitor Number*_____*Study ID*_____

This consultation should last no longer than 10 minutes. It is meant to be a follow up on the previous medication counselling to find out whether any strategies to help with medication taking have been successful.

Problem Category	Was a strategy agreed to address this problem? (please tick)	Has the strategy been followed?	If not, for what reason?	If YES, was the stragegy successful?	In what way was the strategy successful or not successful? (please describe and complete below if not enough space)
Side effects		Y / N		Y / N	
Size or taste of tablets		Y / N		Y / N	
Number of doses a day		Y / N		Y / N	
Non-acceptability		Y / N		Y / N	
Forgetfulness		Y / N		Y / N	
Non-comprehension		Y / N		Y / N	
Total number of different tablets		Y / N		Y / N	
Any new problems? (please describe)					
Anything else not covered by the above problem areas or further comments (please state)					

Appendix 6 Flow chart for choosing the drug for use in the electronic monitor

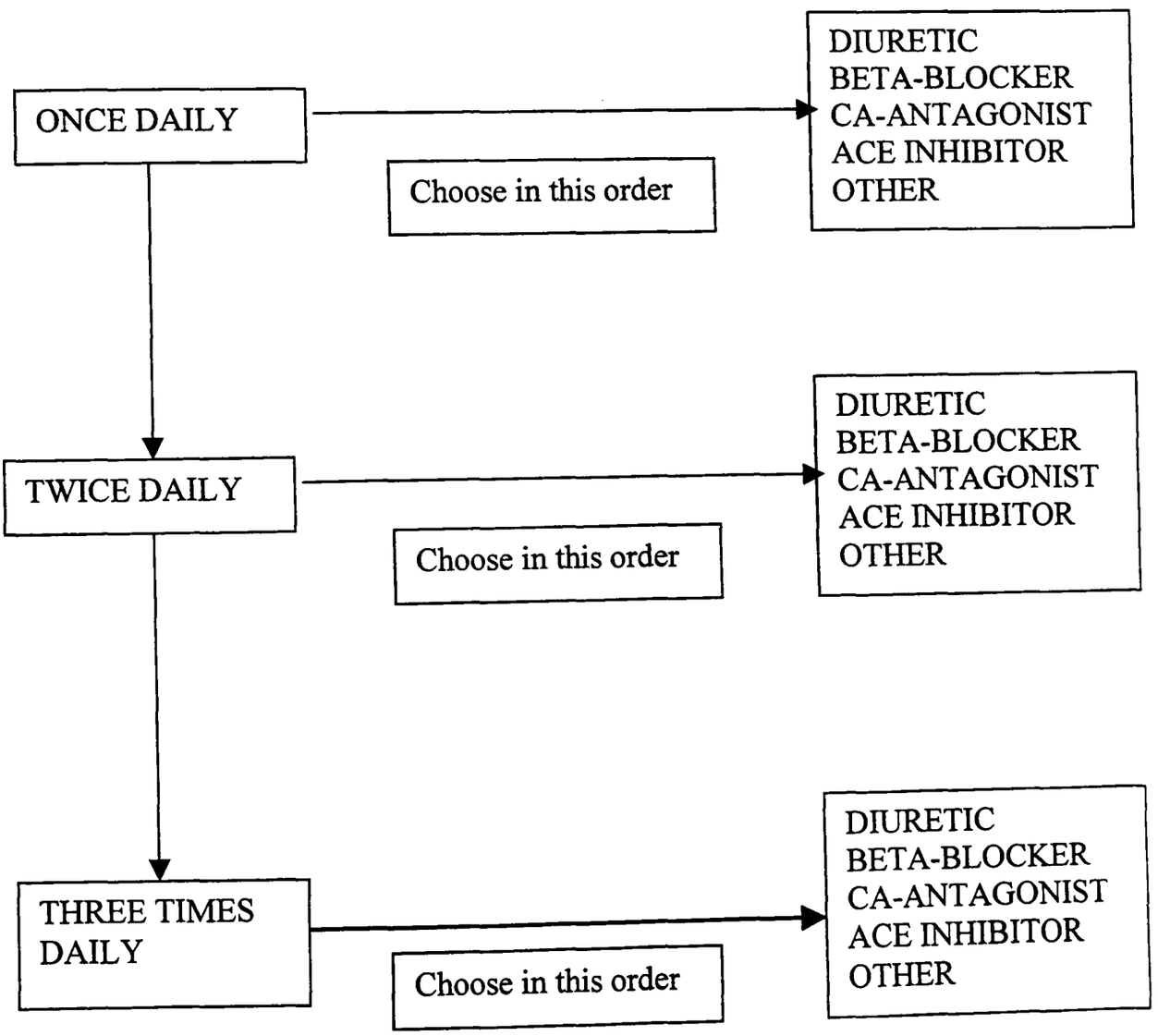
Blood pressure medication adherence study

How to choose the blood pressure tablet for the monitor:

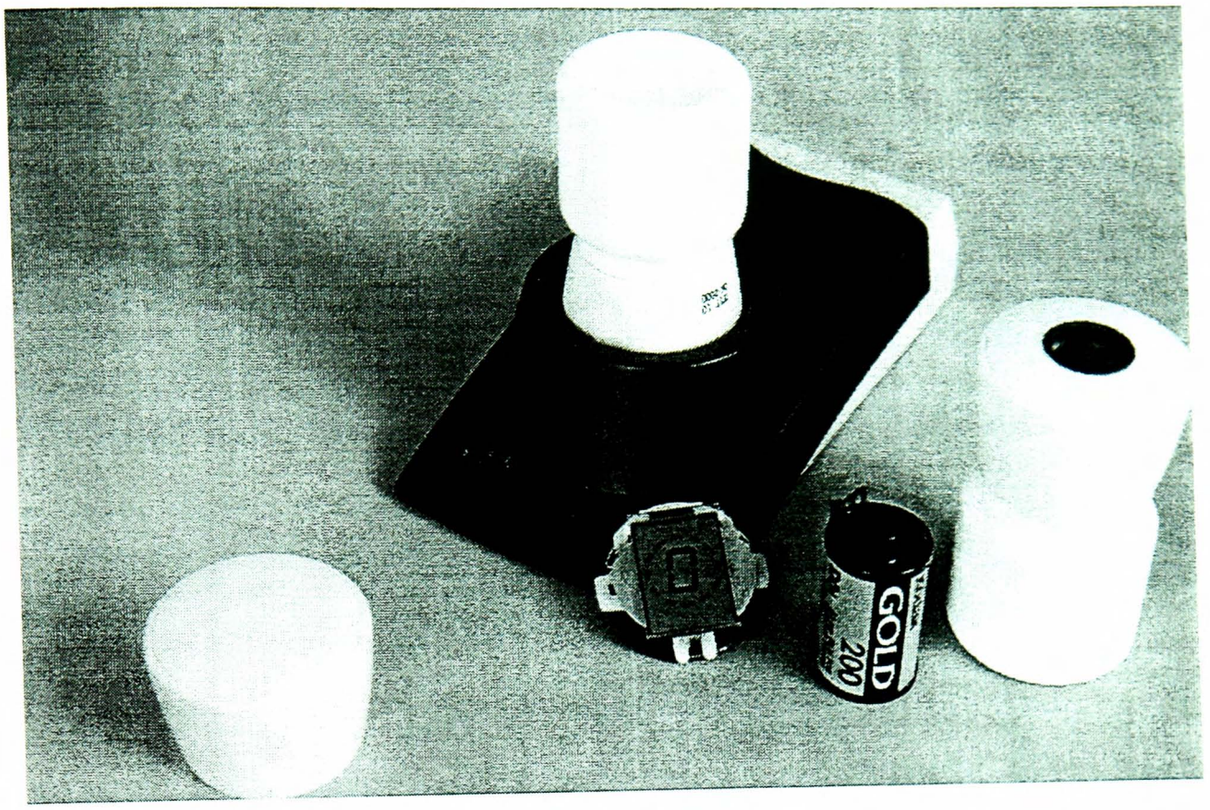
During this study patients will only take <u>one type of blood pressure tablet</u> out of the electronic containers.

If patients are on a <u>more than one blood pressure tablet</u>, you will need to choose the drug that has to go into the container.

Please <u>choose the drug according to the hierarchy below</u> (once daily before twice daily before three times daily, and diuretics before beta-blockers before Calcium antagonists before ACE inhibitors before others).



Appendix 7 Photo of equipment used: Electronic monitor and downloading port



Appendix 8 Patient information on MEMS electronic monitors

Name_____

How to use the special tablet container

In order to learn more about dosing patterns in people who are prescribed blood pressure lowering tablets, we are providing you with a special tablet container **(MEMS-container).** This tablet container has an electronic watch in its screw-top closure. Thus we can register the date and time you open the bottle for taking your tablets.

When using the MEMS-container, please pay attention to the following:

- **Your doctor has prescribed you _____ . Whenever you get a new prescription for these tablets, please take them out of the original packet and transfer them into the MEMS-container (preferably at the time when you would take a dose out anyway)**
- **Take _____only out of this MEMS-container.**
- **Open the MEMS-container only when you intend to take a tablet of _____.**
- **Close the MEMS-container promptly after removing a tablet of _____.**
- **Never leave the MEMS-container open.**
- **If for any reason there is a change in the pattern of your pill-taking (for example, due to a holiday, moving house, sudden illness etc.) we would be grateful if you could make a note in a little note book or on a sheet of paper and bring it with you to the next nurse appointment**
- **If _____ is being stopped by your GP, please contact the practice nurse to tell you which other blood pressure tablet you should put in the container instead**

Please take your MEMS-container with you whenever you see the nurse at the surgery and return it at the end of the study.

Many thanks for your co-operation! We hope that taking part in this research will be interesting and rewarding for you. Please do not hesitate to contact Dr Schroeder (0117 928 7318) or your practice nurse at the surgery if you have any questions or would like further information.